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BASAL HEAT PRODUCTION IN RELATION TO GROWTH

A LONGITUDINAL STUDY ON NORMAL INFANTS SIX TO TWENTY MONTHS OF AGE

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AND

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Most of the knowledge concerning basal heat production in infants 6 to 20 months of age has been derived from the classic study of Benedict and Talbot [1] in 1921. These investigators in the course of a study of basal metabolism from birth to puberty made repeated observations on a large group of infants whose ages ranged from 6 to 20 months. In one instance as many as fifteen tests were performed on 1 subject during this period. Subsequent analyses of these data by a number of authors [2] indicated that at a point near the end of the first year of life an irregularity in heat production occurs. Opinion has differed, however, as to the role played by changes of growth rate in the production of this phenomenon and as to its relation to the increased metabolism of childhood. The principal obstacle to a solution of the problem appears to have been the relatively wide scatter characterizing the data.

Since the changes involved in the processes of growth differ in different persons and occur at varying times, it would appear that repeated observations on a single infant should yield data with greater internal consistency than the same number of single observations on different infants. Since the longitudinal data of Benedict and Talbot do not provide satisfactory information because they are few and widely spaced,

From the Normal Child Development Study of the Department of Pediatrics, College of Physicians and Surgeons, Columbia University.

1. Benedict, F. G., and Talbot, F. B.: The Physiology of the New-Born Infant: Character and Amount of the Katabolism, Publication 233, Carnegie Institution of Washington, 1915; Metabolism and Growth from Birth to Puberty, Publication 302, Carnegie Institution of Washington, 1921. Benedict, F. G.: Boston M. & S. J. **181**:107, 1919.

2. (*a*) Levine, S. Z., and Marples, E.: The Respiratory Metabolism in Infancy and Childhood, Am. J. Dis. Child. **41**:1332 (June) 1931. (*b*) Adams, T. W., and Poulton, E. P.: Guy's Hosp. Rep. **87**:107, 1937. (*c*) Wetzel, N. C.: J. Pediat. **4**:465, 1934.

they have been treated in most analyses from a cross-sectional standpoint only.

Recently, since the completion of the present work, a longitudinal study has been reported [3] in which monthly observations were made on 8 infants between the ages of 3 and 15 months. The results of this investigation will be discussed.

The facilities of the Normal Child Development Study presented an unusual opportunity to make repeated observations on individual infants. The number of subjects selected for study was small; this permitted a large number of tests on each. It was hoped that this approach would have the advantages which are derived from examination of a small microscopic field under high magnification as compared with the more diffuse but less well defined low power view of the field as a whole.

In all, 217 successful tests were made on 2 infants over a period of fourteen months, and 39 further observations were made on 2 other babies over much shorter periods. For each of the first 2 subjects sufficient data were available for individual biometric analyses of the relation of heat production to age, to weight, to height, to surface area and to body thickness.[4]

Specifically, answers were sought to the following questions:

1. What is the day to day variation in heat production for 1 infant, and is this variation constant throughout the period from 6 to 20 months?

2. Which measure of growth—weight, height, surface area or body thickness—increases most consistently with the increase in heat production in the same subject?

3. Is there any systematic trend or any irregularity in the relationships between metabolism and growth in an infant between 6 and 20 months of age?

PLAN OF STUDY

Experimental Subjects.—One girl and 2 boys were the experimental subjects. A fourth baby (a boy) was studied for only two months. The infants were all apparently healthy. They all came of poor families.

C. H., the only girl, was a mulatto. She was well nourished, happy and bright and an unusually cooperative and placid baby. A. C. was a mulatto. He was well nourished, cooperative and of a rather boisterous type. J. D. was of Irish descent. He was badly neglected at home and was the only subject whose state of nutrition was only fair. He was uncooperative, irritable, unhappy and tense. At no time, even during sleep, did he appear relaxed. His naps were usually short and restless. As a result, a large proportion of his tests had to be discarded. The total span of study on this infant was only nine months, owing to the onset of a protracted illness. J. S. was of Irish descent. He was studied only between the ages of 6 and 8 months. He was a well nourished, docile and placid infant.

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3. Clagett, D. D., and Hathaway, M. L.: Basal Metabolism of Normal Infants from Three to Fifteen Months of Age, Am. J. Dis. Child. **62**:967 (Nov.) 1941.

4. Body thickness was expressed as $\sqrt{\frac{\text{weight}}{\text{height}}}$.

Chart 1 shows the weight curves for C. H. and A. C., the 2 infants studied for the longest periods. Smooth curves calculated by the method of Weinbach [5] are included in the figures to show the normal course of growth in weight exhibited by the infants.

Routine.—The babies were brought to the clinic by a nurse, usually at 10 o'clock on the morning of the test, after having been fed at home at about 8 a. m. It was

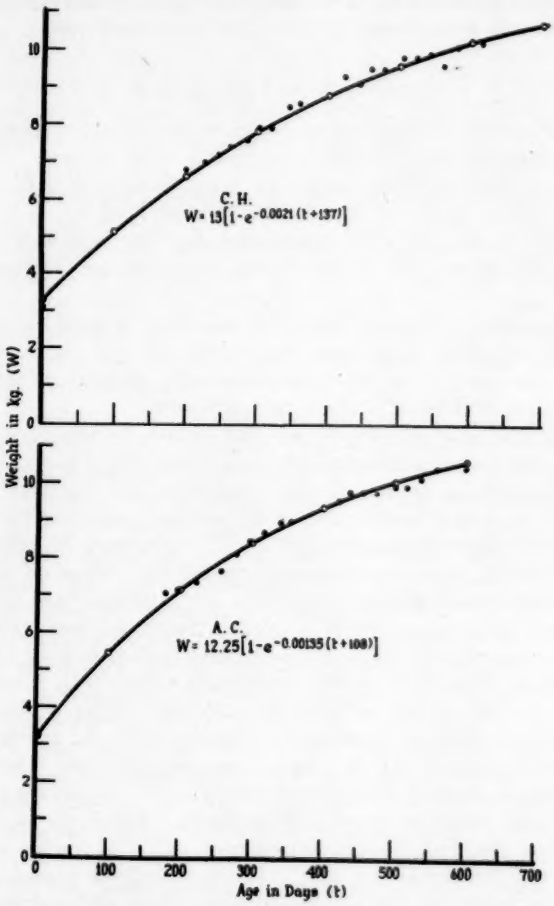

Chart 1.—The course of growth in weight of the 2 infants C. H. and A. C. Charted points represent the mean value of several successive weighings. Points on the smooth curve were calculated from the equations given below each curve.

planned that observations be made on each child three times a week. This was not always feasible, but only rarely did periods of more than a week elapse for any 1 child without a test.

5. Weinbach, A. P.: The Human Growth Curve: I. Prenatal; II. Birth to Puberty, Growth **5**:217 and 235, 1941.

On arrival at the clinic the infants were undressed, weighed, and bathed if necessary, and their rectal temperatures were recorded. In no case was a metabolism test performed on a subject whose temperature exceeded 100 F. After being dressed, the infants played in the nursery until tested. No restrictions were placed on their activity during this time.

Determinations on 2 babies were usually made each day. The first infant was taken to the metabolism room at about 10:30 or 11 a. m. The second child was fed between 11 and 11:30 and was taken to the metabolism room between 1:30 and 2 p. m. The order in which the infants were tested on any day was purposely random. Height was usually measured after the metabolism test.

METHODS AND APPARATUS

An attempt was made to duplicate as closely as possible the careful technic used by Lewis, Kinsman and Iliff [6] in their longitudinal study of older children. The method was described by these authors in great detail, and only those points involving some difference in technic will be mentioned here.

The open-circuit-type chamber calorimeter had the following dimensions: 35 by 101.1 by 45.7 cm. The inside volume, corrected for mattress, etc., was 131.4 liters.

Gas samplers, both of the all glass kind described by Lewis and others and of the usual mercury-containing type, were used. A few drops of water was always kept in the samplers to insure continued saturation of the gas. Calculations were made on the basis of 100 per cent saturation.

In the determination of carbon dioxide and oxygen by the Carpenter method a 10 per cent solution of potassium hydroxide containing 1 per cent of sodium taurocholate was used for carbon dioxide absorption. All joints between rubber and glass in the apparatus were coated with caulking material to prevent leaks. The apparatus and reagents were checked about once a week by analyses of outdoor air. Fifty-eight such measurements yielded the following results. The averages with their standard deviations were: for carbon dioxide, 0.036 ± 0.0058 volumes per cent; for oxygen, 20.939 ± 0.0229 volumes per cent. One of a pair of duplicate samples of outdoor air was sometimes collected from the gasometer after having passed through the empty, closed calorimeter. This procedure served to detect leaks in the system as a whole. Alcohol checks of the respiratory quotient were performed only occasionally. Of 24 checks the average was 0.665 with a standard deviation of 0.0137. In 3 instances these tests were arranged in the following manner so as to simulate the conditions of a metabolism test: Three samples of air were taken, so timed that equilibrium within the calorimeter was not attained when the first aliquots were drawn off. The carbon dioxide thus increased from one sample to the next. The fact that the respiratory quotient remained constant within the limits of experimental error was interpreted to mean that under the conditions of the test mixing of the air in the calorimeter was adequate.

For the measurement of height the infant was laid on his back on a table along one side of which was attached a centimeter steel rule. The head was held straight, in contact with a stationary headboard. The knees were kept extended while a movable footboard was brought against the soles of the feet. The position

6. Lewis, R. C.; Kinsman, G. M., and Iliff, A.: Basal Metabolism of Normal Boys and Girls from Two to Twelve Years Old, Inclusive, Am. J. Dis. Child. **53**:348 (Jan., pt. 2) 1937.

of the footboard on the measuring rod indicated the child's height. Readings were repeated until two agreed. The method appeared to be accurate to within about 1 cm.

Technic of Metabolism Test.—Heat production was always measured during sleep. The times when the child entered the calorimeter and when he fell asleep were recorded on the data sheet. The interval was seldom more than twenty minutes and frequently less than five.

Records were also kept of the child's clothing, which varied with the room temperature. The estimated volume of the clothing was applied as a correction to the volume of the calorimeter in calculating heat production.

In hot weather the temperature inside the calorimeter was kept from rising above that of the room by means of a large closed can of cracked ice through which the incoming air passed just before it entered the calorimeter. This device also helped to reduce the humidity inside the calorimeter.

When the child was asleep, the lid of the calorimeter was closed and the time was recorded. For a period, usually of about seven minutes (varying with the size of the child and the degree of relaxation), the speed of the fan was kept at a slower rate than was used throughout the remainder of the test. This procedure hastened the establishment of gaseous equilibrium. Between five and twenty minutes later, the first sample of air was taken. Two subsequent samples were taken at intervals of about six or eight minutes. The sampling period was usually two minutes. The entire test lasted from thirty minutes in some instances to an hour and a half in others.

By means of mirrors placed at two points in the room at proper angles to the glass door in the calorimeter lid it was possible for a single operator to observe the subject almost continuously without interfering with the child's falling asleep or with the collection of samples of air. All movements were recorded and formed the basis for grading the tests.

A test was classified by the letter A when there was complete lack of motion throughout the entire period embraced by the collection of the three samples. A classification of B was given under three conditions: (1) when slight movements only (twitching of lips or fingers or a fleeting smile) were observed; (2) when a single large motion (turning the head or moving an arm or leg) occurred either less than five seconds before the end of a sampling period or (3) between samplings but at least ten minutes before the following sample was taken. A test classified by the letter C was one in which, because of motion, only two instead of three satisfactory samples could be secured. Tests were discarded if more motion occurred than that described under these headings.

Of the tests which were accepted as satisfactory, 42 per cent were A, 27 per cent B and 31 per cent C. Approximately 15 per cent of the acceptable tests had to be discarded later because of technical difficulties with the Carpenter apparatus.

Calculation.—Heat production was calculated from carbon dioxide output. In all instances in which a systematic change in the carbon dioxide content of the three samples indicated that gaseous equilibrium had not been reached during the test, this was corrected for by the method of Higgins and Bates.[7] Since this correction is determined from the curve describing the change in the carbon dioxide content of the calorimeter air, a relatively long interval (six to ten minutes) between the collection of samples was allowed in the present study in order to permit greater accuracy in the appraisal of the shape of this curve.

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7. Higgins, H. L., and Bates, V.: New Method for Determination of Basal Metabolism of Babies and of Small Children, Am. J. Dis. Child. **39**:71 (Jan.) 1930.

In the case of C tests, i. e. those in which only two samples were available, the method of calculation was as follows: Unless the two values for carbon dioxide concentration agreed, they were plotted against time in the usual manner for the Higgins and Bates method and the calories at equilibrium were computed from the second value as if a third analysis had been obtained and the result found to lie on a straight line with the other two. The correction involved in this assumption errs on the side of being too great. Accordingly, a second calculation of calories was made on the basis of the same (second) carbon dioxide value, with no correction, i. e. on the assumption that the hypothetic third analysis would have yielded a carbon dioxide value identical with the second. The correction in this case (zero) probably errs on the side of being too small. The two calculations thus yielded values with errors which tended to cancel out, and their average was taken to represent an approximation of the true heat production.

Of the three air samples only one or two were analyzed for oxygen, and from these values the respiratory quotient was obtained.[8] In this calculation as well as in the computation of calories, the carbon dioxide and the oxygen content of the incoming air were taken to be represented by the final average of all of the analyses of outdoor air ($CO_2 = 0.036$ per cent; $O_2 = 20.939$ per cent).

Since it was not feasible to obtain twenty-four hour samples of urine, the usual assumption was made that 15 per cent of the calories were derived from protein. Respiratory quotients higher than 0.96, and thus inconsistent with this assumption, were sometimes obtained. They were considered erroneous and replaced in the calculations by the average respiratory quotient for the particular child. The error involved was small.

BASALITY

The conditions obtaining in these experiments satisfy the requirements for basality in some respects less well and in others better than those more usually employed.

Food.—It was not possible to observe fasting conditions, nor was it feasible to standardize the technic as to time after feeding or size or content of the last meal, since this was often eaten at home. The tests were performed one to five hours—usually at least two hours—after the previous meal. Within these limits, time after the last meal did not appear to influence the height of basal heat production (chart 2).

Depth of Sleep.—Since the metabolism tests were in all cases begun during sound sleep and continued for considerable periods, it is probable that the leveling off of basal metabolism described by Day[9] had already occurred before the last sample of air was taken. Compared with results obtained for subjects who are awake or who have just fallen asleep, the values yielded by the present method undoubtedly are unduly low—a factor which might tend to compensate for the stimulating effect of food.

Motion.—Although almost continuous observance of the child was possible by means of the mirrors, periods as long as two minutes some-

8. Occasionally no oxygen determination could be made and the average respiratory quotient for the infant in question had to be used.

9. Day, R.: Effect of Sleep on Insensible Respiration in Infants and Children, Am. J. Dis. Child. **58**:82 (July) 1939.

times elapsed when the subject could have made an unobserved motion. The long interval between taking of samples tended to permit reestablishment of gaseous equilibrium, in spite of the relatively large amount of "dead" air space in the calorimeter. Moreover, after analysis, detection of an undue increase in carbon dioxide in one sample due to motion was usually easy, and the period could be eliminated.

Psychic Factors.—Owing to the frequency with which the tests were made, psychic disturbances were negligible. After a short training period all of the infants came to regard the procedure as part of a familiar routine. The tests were performed at times which coincided with their usual napping hours, and the drone of the motor seemed to lull them to sleep.

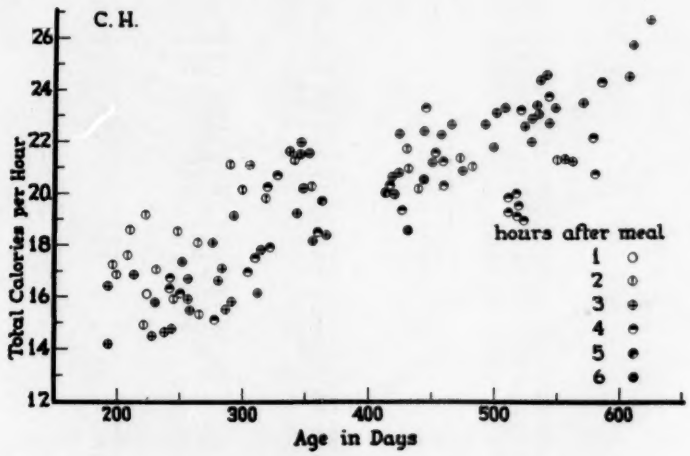

Chart 2.—The relation for infant C. H. between total calories per hour, the age of the infant and the interval between feeding and performing the test. The random distribution of points corresponding to specific intervals against the background of all the points shows that variations in the interval did not exert an important effect on the total heat production.

In table 1 the basic data are presented in the form in which they were calculated from the metabolism tests.

INTERPRETATION OF RESULTS [10]

1. What is the day to day variation in heat production?

10. The statistical formulas used in interpreting the results of the metabolism tests are given in most textbooks on biometry. Whenever necessary, the formulas as published were modified to conform with the concept of degrees of freedom as described by R. A. Fisher. All formulas used in the analysis are contained in the following reference volumes: Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, Oliver & Boyd, 1934. Dunn, H. L.: Physiol. Rev. **9**:275, 1929. Garrett, H. E.: Statistics in Psychology and Education, New York, Longmans, Green & Co., 1926.

TABLE 1.—*Repeated Tests of Basal Heat Production in Infants*

Subject	Date	Temperature Inside Calorimeter	Age, Days	Weight, Kg.*	Height Cm.*	Respiratory Quotient	Total Calories per Hour
C. H. ♀	2/5	24.8†	192	6.76	67.2	0.85	16.1
		25.5†	193	6.78	67.2	0.77	14.1
		24.2†	196	6.78	68.5	0.88	17.3
		24.8†	200	6.78	69.4	0.89	16.8
		24.1	208	6.80	68.6	....	17.6
		26.0	210	6.92	68.9	0.80	18.6
		23.9	213	6.86	69.9	0.79	16.9
	3/6	25.8	222	7.12	68.5	0.88	15.0
		26.0	223	7.03	69.6	0.84	19.1
		25.3	224	7.09	69.5	0.96	16.1
		24.1	228	6.90	69.4	0.88	14.4
		25.9	230	6.88	69.3	....	15.8
		26.4	231	6.89	69.4	....	17.0
		25.0	238	7.14	70.6	0.88	14.6
		25.3	241	6.98	70.5	0.87	16.2
		25.8	242	7.19	70.4	0.90	16.6
		25.9	243	7.23	70.5	0.94	14.7
		26.6	244	7.10	69.6	0.82	16.0
	4/1	25.3	248	7.26	69.9	0.83	18.6
		24.9	250	7.28	70.5	0.86	16.0
		25.0	251	7.23	70.5	0.88	17.5
		27.0	256	7.24	69.7	0.80	16.7
		24.6	257	7.38	69.7	0.81	15.8
		25.2	258	7.30	70.2	....	15.5
		27.5	263	7.57	71.0	....	15.0
		26.0	265	7.40	71.5	0.82	18.0
		26.0	266	7.48	71.5	0.76	15.4
		24.5	276	7.54	71.5	0.86	18.0
		25.6	277	7.52	71.8	0.86	15.0
	5/3	26.4	280	7.09	72.0	0.83	16.5
		25.4	284	7.66	73.0	0.91	17.0
		24.9	287	7.71	72.5	0.86	15.5
		25.3	290	7.76	73.1	0.83	21.1
		25.1	291	7.77	73.1	0.83	15.8
		24.5	293	7.82	73.6	0.87	19.1
		26.0	300	8.00	73.4	0.87	20.1
		25.0	305	7.77	72.8	....	21.0
		24.5	306	7.94	72.4	0.82	17.0
	6/4	29.1	312	7.71	72.4	....	16.1
		29.6	313	7.88	73.1	....	17.5
		29.2	314	7.94	73.0	0.90	17.6
		24.6	318	7.94	73.5	0.80	19.7
		23.8	319	7.91	73.6	0.85	20.1
		28.4	321	7.88	72.6	....	17.8
		28.0	327	8.00	73.1	0.74	20.6
	7/1	28.2	339	8.35	74.0	0.83	21.4
		26.7	341	8.45	73.3	0.86	21.2
		26.3	343	8.52	74.3	0.90	19.1
		29.3	346	8.65	74.6	0.93	21.9
		28.6	347	8.62	74.9	....	21.4
		30.0	349	8.67	75.0	0.90	20.2
		26.5	353	8.62	73.0	0.87	21.5
		27.0	354	8.62	74.3	0.85	20.2
		26.8	356	8.62	74.3	0.89	18.1
		30.3	360	8.69	76.2	0.78	18.4
		28.7	363	8.67	74.0	0.81	19.6
		30.1	367	8.62	76.1	0.92	18.3
	9/16	25.8	416	9.24	77.3	0.97	20.1
		26.2	419	9.18	78.6	0.88	20.5
		28.0	420	9.13	75.8	0.84	19.9
		27.1	423	9.36	76.9	0.84	20.7
		27.7	425	9.30	77.8	....	22.2
		23.7	426	9.30	76.5	0.81	19.2
		24.7	430	9.41	76.1	0.91	21.6
		27.6	431	9.41	77.3	0.85	18.5
	10/2	26.9	432	9.41	77.1	0.85	20.9
		25.7	440	9.49	76.8	0.93	20.1
		26.1	444	9.44	77.6	0.83	20.4
		26.0	445	9.53	77.6	0.86	22.3
		25.2	446	9.53	76.6	0.83	23.2
		27.2	451	9.44	76.7	0.83	21.3
		27.7	453	9.64	76.6	....	21.2
		26.6	458	9.64	78.5	0.86	21.2
		24.2†	459	9.48	77.7	0.91	22.2
		24.9	460	9.61	77.3	0.82	20.2
	11/6	27.4	467	9.64	78.0	0.88	22.6
		28.1	473	9.58	77.8	0.83	21.3
		27.2	474	9.58	78.8	0.83	24.5
		27.1	476	9.58	77.5	0.86	20.8
		28.0	483	9.53	79.3	0.87	21.0

TABLE 1.—*Repeated Tests of Basal Heat Production in Infants—Continued*

Subject	Date	Temperature Inside Calorimeter	Age, Days	Weight, Kg.*	Height Cm.*	Respiratory Quotient	Total Calories per Hour
	12/2	26.8	493	9.75	78.8	0.86	22.6
		28.2	500	9.70	78.8	0.83	21.8
		28.1	502	9.93	79.5	0.85	23.0
		28.0	509	9.66	79.3	0.85	23.4
		27.2	510	9.75	79.8	0.84	19.7
		27.9	511	9.75	79.2	0.90	19.2
		26.8	515	9.89	79.9	0.78	19.9
		27.3	517	9.75	79.3	0.88	19.2
		26.8	518	9.86	79.1	0.94	19.3
		27.0	521	9.64	80.2	0.83	23.2
		26.7	522	9.64	80.0	0.84	18.9
	1/2	26.8	524	9.82	80.1	0.89	22.5
		28.5	530	9.64	80.5	0.84	22.0
		29.5	531	9.75	80.6	0.83	22.8
		27.8	535	10.12	80.4	0.81	23.6
		27.4	536	10.12	80.4	0.83	23.0
		28.4	538	9.66	80.8	0.83	24.3
		28.2	542	9.89	80.7	0.82	24.5
		28.8	543	9.50	....	0.82	23.6
		28.6	544	9.92	80.6	0.73	22.7
		27.5	549	10.26	80.5	0.75	23.3
		28.3	551	9.86	80.6	....	21.2
	2/3	29.2	556	9.64	80.5	0.72	21.3
		27.2	563	9.13	81.0	0.81	21.2
		27.5	571	10.01	81.6	0.84	23.4
		26.6	579	9.98	82.3	0.78	22.1
		27.4	580	10.02	82.4	0.84	20.7
	3/4	27.1	585	10.32	....	0.81	24.2
		27.3	609	10.09	81.0	....	24.5
		27.3	612	10.09	80.6	....	25.6
	4/7	27.3	619	10.38	81.5	....	27.5
		28.6	626	10.44	82.3	0.86	26.5
A. C. ♂	1/15	24.5†	167	6.99	64.5	0.84	17.8
		23.0†	168	7.03	66.3	0.83	13.2
		24.0†	177	7.12	66.7	0.77	16.6
		25.4†	182	6.97	66.9	0.78	13.7
		22.7†	183	6.82	67.7	0.83	15.0
	2/1	24.5†	184	7.06	68.1	0.82	16.2
		24.1†	185	7.13	66.2	0.85	11.6
		24.8†	188	7.17	67.0	0.91	12.0
		25.0†	191	....	67.9	0.82	14.8
		24.2†	192	6.86	67.7	0.80	17.4
		24.8†	196	7.06	67.6	0.89	17.5
		26.5	203	7.34	68.4	0.92	14.4
		24.7	209	7.46	69.0	0.83	14.2
		26.1	212	7.12	70.8	0.83	15.1
	3/12	25.3	224	7.20	69.9	0.82	16.6
		25.7	226	7.26	70.1	0.89	12.0
		26.1	230	7.42	70.0	0.92	15.4
	4/4	25.5	247	7.10	71.6	0.94	13.4
		24.7	251	7.64	69.3	....	13.9
		25.0	253	7.80	....	0.84	15.8
		25.7	254	7.74	70.4	0.84	13.9
		26.0	259	7.54	70.5	....	13.3
		25.4	266	8.05	70.4	0.93	15.4
		26.3	269	7.88	70.6	0.92	12.8
		26.0	273	8.02	70.4	0.87	17.3
	5/6	25.6	279	8.16	72.0	0.94	13.4
		26.3	280	8.32	72.3	0.96	16.8
		24.6	282	....	72.8	0.81	17.4
		25.9	287	8.46	71.6	0.96	19.3
		23.5	288	8.42	71.0	0.95	17.3
		25.3	289	8.33	73.2	0.89	18.9
		23.5	293	7.82	72.8	....	19.8
		25.4	294	8.56	72.1	....	17.1
		24.3	296	8.62	70.8	....	17.1
		25.5	300	8.45	72.3	0.74	19.4
		26.6	301	8.64	73.5	0.88	17.8
		24.8	304	8.51	72.4	0.93	16.2
	6/3	26.9	307	8.68	72.5	0.78	16.2
		28.6	308	8.68	72.3	0.87	18.7
		28.9	310	8.62	74.4	0.85	16.8
		24.9	315	8.45	73.3	0.73	18.5
		29.3	317	8.56	73.6	0.99	17.1
		26.9	321	8.56	73.1	0.86	18.8
		25.9	322	8.56	72.4	0.98	18.1
		28.7	323	8.45	73.6	....	18.4
	7/1	25.9	335	8.86	73.6	....	16.4
		26.4	336	8.90	72.6	0.73	17.4

TABLE 1.—*Repeated Tests of Basal Heat Production in Infants—Continued*

Subject	Date	Temperature Inside Calorimeter	Age, Days	Weight, Kg.*	Height Cm.*	Respiratory Quotient	Total Calories per Hour
		26.2	337	8.86	73.8	0.76	19.8
		29.0	342	8.99	74.0	0.97	17.6
		29.8	343	9.16	74.1	....	17.3
		27.3	349	9.50	74.7	0.79	22.1
		26.4	350	9.01	74.3	0.78	20.1
		26.0	351	8.67	73.4	0.73	19.9
		31.5	356	8.87	73.6	....	17.0
		28.6	357	8.96	74.2	0.80	22.9
		28.1	358	8.92	75.6	0.71	16.9
	9/16	24.6	412	9.41	77.0	0.95	17.1
		27.8	420	9.70	78.3	0.99	23.1
		26.5	421	9.36	76.8	0.98	18.9
		23.0	426	9.67	77.7	0.96	19.9
	10/2	26.9	428	9.91	77.6	0.86	19.6
		25.2	433	9.68	77.7	0.84	21.6
		25.1	436	9.95	77.2	0.80	19.4
		25.3	441	9.70	77.8	....	22.0
		26.1	442	9.61	78.5	0.85	21.5
		25.7	447	9.77	77.7	0.80	23.0
		24.8	448	9.78	77.9	0.77	19.8
		27.1	450	9.64	77.9	0.79	22.4
		27.0	454	9.70	77.9	0.86	20.2
		26.5	455	9.75	78.5	0.84	19.0
		26.5	456	9.66	78.2	0.84	19.6
	11/4	25.9	461	9.81	78.9	0.82	17.2
		27.8	463	9.98	78.0	....	20.4
		28.4	469	9.98	78.7	0.91	20.8
		25.0†	472	9.70	77.4	0.85	21.6
		27.6	479	9.47	78.8	0.73	20.8
	12/3	27.9	490	9.70	79.3	0.91	18.0
		27.7	497	9.58	79.3	0.86	19.6
		27.5	498	10.12	78.9	0.88	20.3
		27.4	499	9.98	78.6	0.74	20.6
		28.3	505	10.10	79.3	0.79	22.3
		27.9	506	9.98	....	0.84	21.0
		28.6	507	9.92	....	0.78	21.8
		27.5	511	9.98	78.5	....	23.2
		27.1	514	9.81	80.4	0.80	19.8
	1/2	26.1	520	9.92	80.1	0.78	20.0
		28.1	526	9.95	80.1	0.90	19.8
		29.5	527	9.98	80.3	0.92	22.2
		28.0	528	10.06	80.1	0.85	21.6
		27.2	531	10.15	80.2	0.81	20.2
		27.1	532	10.26	80.3	0.82	23.9
		27.2	534	10.01	80.5	0.81	21.4
		27.3	538	9.86	80.9	0.80	19.7
		28.6	539	10.09	80.3	0.78	24.0
		28.8	540	10.43	80.2	0.88	23.0
		26.6	545	10.44	80.8	0.85	20.5
		27.3	548	10.20	81.1	0.80	21.4
	2/3	28.2	552	10.49	80.5	0.84	21.9
		27.2	559	10.43	80.5	0.83	22.1
		27.5	566	10.49	80.5	0.79	25.8
		27.5	573	10.26	81.8	0.80	22.2
	3/3	27.5	580	10.46	81.6	0.79	25.2
		27.8	605	10.46	82.1	0.92	22.1
		26.8	608	10.43	82.3	....	23.8
	4/7	27.3	615	10.49	82.3	....	22.5
J. D. ♂	1/5	23.2†	192	6.80	64.5	0.76	14.8
		22.0†	196	6.98	65.5	0.87	20.6
		24.5†	202	6.98	66.1	0.73	16.6
		23.0†	208	6.70	65.1	0.76	19.2
		23.0†	211	6.92	66.4	0.78	18.8
	2/6	25.5†	224	7.06	68.0	0.83	17.8
		24.5†	233	6.98	67.3	0.74	20.4
		26.5	238	6.95	68.0	0.85	21.6
	4/1	24.4	279	6.98	69.7	....	17.5
		25.3	280	7.26	68.8	....	17.6
		25.8	281	7.23	71.0	....	20.9
		27.3	297	7.47	70.1	0.96	17.2
		25.2	300	7.71	70.0	0.90	17.4
		26.0	307	7.77	71.2	0.95	18.1
	5/3	26.0	311	7.68	69.7	0.85	19.7
		25.1	314	7.81	70.0	....	14.6
		24.4	318	7.81	69.4	....	18.8
		24.1	321	7.77	70.5	0.81	17.7
		24.5	323	7.88	72.0	0.91	19.2
		22.8	330	8.00	72.3	0.85	21.5
		26.8	332	8.00	72.3	0.91	17.5

TABLE 1.—*Repeated Tests of Basal Heat Production in Infants—Continued*

Subject	Date	Temperature Inside Calorimeter	Age, Days	Weight, Kg.*	Height Cm.*	Respiratory Quotient	Total Calories per Hour
		27.0	335	7.88	....	0.81	20.8
	6/3	27.7	342	7.60	71.3	....	16.2
		30.7	344	8.16	72.4	....	21.2
		24.9	349	7.88	72.3	0.84	20.1
		26.5	356	8.11	71.9	....	22.7
	7/5	26.6	374	8.01	73.0	0.89	21.5
		26.3	386	7.77	71.0	0.74	22.9
		27.7	387	8.10	71.0	0.90	19.8
		28.3	393	8.22	73.0	0.80	15.1
	9/19	27.2	450	8.41	74.3	0.94	20.5
		24.8	457	7.40	74.3	0.85	21.0
J. S. ♂	1/4	26.0	183	7.43	68.4	0.83	15.0
		27.2	184	7.48	68.5	....	15.0
	2/11	26.8	221	7.37	68.8	0.84	15.7
		25.9	223	7.54	68.4	0.83	16.3
		25.6	227	7.57	68.0	0.80	17.8
		25.8	228	7.70	68.0	0.86	16.2
		25.9	235	7.88	71.4	0.89	13.8
	3/4	26.8	242	7.91	65.5	0.83	18.3

* The observed weights and heights were average for a period of twenty days, and a smoothed curve was drawn from them. The values recorded in this table and used in the subsequent statistical analyses were derived from these smoothed curves.

† Room temperature.

In table 1 and in chart 3 it may be seen that the difference in basal heat production from one day to the next was often large. Expressed in terms of calories, the differences continued to be of approximately the same magnitude throughout the entire age span. Since the heat output steadily increased, it follows that percentage differences correspondingly declined. The following average values for day to day variation bring this out.

C. H. { average difference before 400 days = 1.7 calories (9%)
       { average difference after 400 days = 1.3 calories (6%)

A. C. { average difference before 400 days = 2.4 calories (14%)
       { average difference after 400 days = 2.2 calories (12%)

J. D. average difference before 400 days = 2.5 calories (13%)

J. S. average difference before 400 days = 1.7 calories (10%)

The description of day to day variability in heat output has been given in the foregoing form because it is convenient for the investigator to compare the results of one test with tests immediately preceding and following it by examining the differences between the consecutive values. Such differences, or average differences, are, however, of limited usefulness. A better statistic is one which describes in standard deviation form the distribution of the results of the separate tests about a theoretic line which denotes the true relationship between caloric output and age. Two methods are available for making the computation; both have been used to yield the statistics presented in table 2.

The first method is based on the assumption, which through the limited age range will be shown to be approximately true, that the increase in calories per hour with age can be described by a straight line. The measure of scatter about this trend or regression line is then given by the conventional standard error of estimate, $\sigma_{est.}$. It is clear,

however, that the relationship between calories and age cannot be linear over a long age span and that even for shorter periods $\sigma_{est.}$ will in general tend to overestimate the magnitude of the day to day fluctuations.

TABLE 2.—*Statistical Expressions of Day to Day Variability in Basal Heat Production of Infants* *

Subject	Average Calories per Hr.	1 Standard Error of Estimate of Calories per Hour From Age ($\sigma_{est.}$)	2 Coefficient of Variation ($V_{est.}$) Per Cent	3 Standard Error From Differences ($\sigma_{diff.}$) Calories	4 Coefficient of Variation ($V_{diff.}$) Per Cent
C. H., ♀..... 112 observations	19.78 (σ=2.93)	1.582	8.00 (σ=0.540) (df=110)	1.364 (df=54)	6.92
A. C. ♂..... 105 observations	18.69 (σ=3.20)	1.860	9.95 (σ=0.697) (df=103)	1.985 (df=50)	10.62
J. D., ♂..... 32 observations	19.04 (σ=2.24)	2.181	11.45 (σ=1.473) (df=30)	2.081 (df=13)	10.99
J. S., ♂..... 8 observations	16.01 (σ=1.49)	1.492	9.32 (σ=2.350) (df=7)	1.702 (df=4)	10.63
All infants combined 257 observations	19.13	1.778	9.29 (σ=0.418) (df=250)	1.738 (df=121)	9.10

Methods of calculation were as follows:

* 1. The standard deviation of calories per hour was calculated from the formula $\sigma=\sqrt{\frac{\Sigma X^2}{N-1}}$, in which X refers to the deviation of each value from the mean and N is the number of observations.

2. The standard error of estimate was computed from the formula $\sigma_{est.}=\sigma'\sqrt{1-r^2}$, in which r is the coefficient of correlation between calories per hour and age; σ' was calculated as $\sqrt{\frac{\Sigma X^2}{N-2}}$, since two degrees of freedom, df, are lost when deviations are measured from a straight line. In the case of J. S. there were only 8 observations and the value of r did not differ significantly from zero. For this reason the value of $\sigma_{est.}$ was taken to be identical with the σ of calories per hour, which was determined from seven degrees of freedom.

3. The standard error from differences was computed from the formula $\sigma_{diff.}=\sqrt{\frac{\Sigma d^2}{2n}}$, in which d is the difference between paired values of determinations of calories per hour, the pairs being made up of consecutive observations which were not more than seven days apart; n refers to the number of paired values and likewise equals the number of degrees of freedom.

4. The coefficients of variation, $V_{est.}$ and $V_{diff.}$, were computed from the formulas $V_{est.}=\frac{\sigma_{est.}}{M}\times 100$; and $V_{diff.}=\frac{\sigma_{diff.}}{M}\times 100$, in which M equals the average calories per hour.

5. The standard deviation of the coefficient of variation was calculated as $\sigma_V=\sqrt{\frac{V}{2N}}\sqrt{1+2\left(\frac{V}{100}\right)^2}$

6. The combined standard error of estimate for the observations on all four infants was calculated as follows: $\sigma_{est.}\text{ (combined)}=\sqrt{\frac{\Sigma(\sigma^2_{est.}\times df)}{\Sigma df}}$

Justification for calculating the statistic results from two circumstances. First, from the standpoint of accuracy or number of statistical degrees of freedom available for the computation, the fullest use is made of all the observations. Second, when, as in the next section, the relationship between calories and other measures of growth, such as age, height or

surface area, is to be investigated by the method of fitting straight lines, the statistic furnishes a basis for comparison. For the latter purpose the scatter described by $\sigma_{est.}$ must be expressed in percentage form, that is,

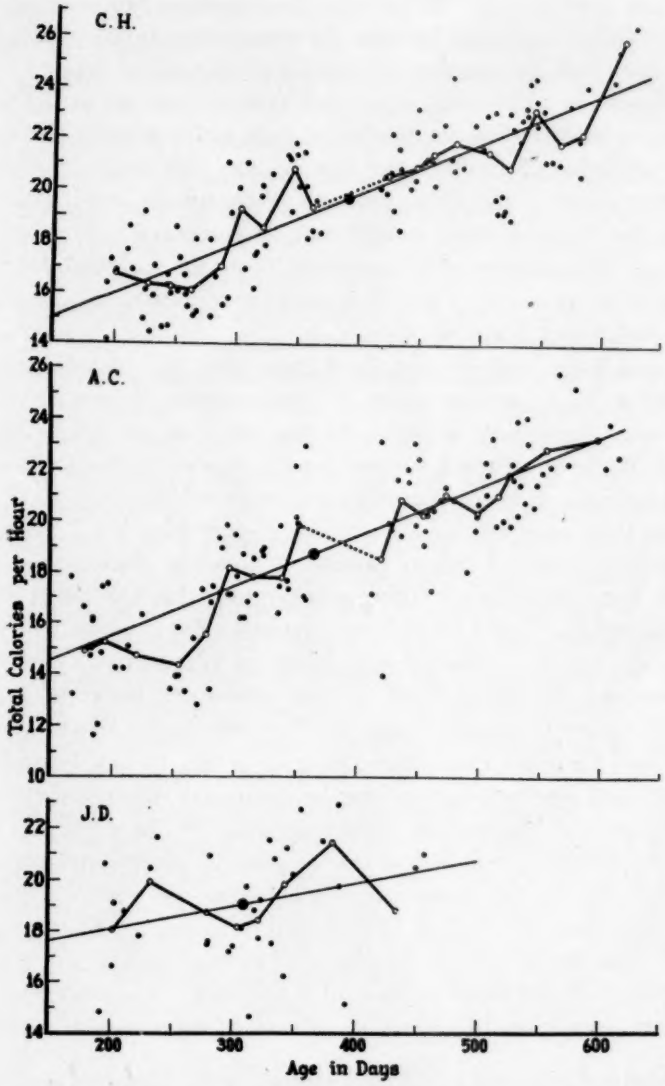

Chart 3.—The relation between total calories per hour and age. (The chart of the data for infant J. D. illustrates the difficulty of establishing reliable correlations between heat production and measures of growth when day to day fluctuations are large and when the period of growth is short. In this as in subsequent graphs the straight line was charted from the regression equation fitted to the data by the method of least squares. The crooked line connects the periodic averages which were used in the tests for linearity of regression.)

as a coefficient of variation, $V_{est.}$. $V_{est.}$ is obtained by dividing $\sigma_{est.}$ by the average total calories per hour and multiplying by 100.

The second method of portraying the day to day fluctuations in statistical form is independent of the shape of the trend line relating calories per hour to age. It has the disadvantage, however, of somewhat diminished accuracy, because the expression so derived is based on less than half the number of statistical degrees of freedom which could be used in calculating $\sigma_{est.}$. An arbitrary period of seven days is chosen as representing an interval during which growth can be considered negligible in relation to day to day variability. From the differences within consecutive pairs of observations within the seven day limit the statistic being sought can be computed. To distinguish it from $\sigma_{est.}$ this statistic will be referred to as the standard error from differences, or as $\sigma_{diff.}$. From it a coefficient of variation, $V_{diff.}$, can be computed, which is analogous to $V_{est.}$.

For rectilinear relationships it is clear that $\sigma_{est.}$ versus $\sigma_{diff.}$ and $V_{est.}$ versus $V_{diff.}$ are estimates in similar form of the day to day fluctuations. Agreement between the respective values can be expected within the limits of accuracy imposed by the degrees of freedom available for computation. For significantly curvilinear relationships $\sigma_{est.}$ should be greater than $\sigma_{diff.}$ and $V_{est.}$ should be greater than $V_{diff.}$. The combined evidence from all infants in table 2 does not disclose appreciable deviation from linearity of regression through the age range studied. The combined $\sigma_{est.}$ based on 257 observations (250 degrees of freedom) is 1.778 calories; the combined $\sigma_{diff.}$ based on 121 degrees of freedom is 1.738 calories. Similarly there is close agreement between $V_{est.}$ and $V_{diff.}$, the respective values being 9.29 per cent and 9.10 per cent.

It should be noted that these measures of day to day fluctuation in recorded basal heat production can be compared directly with similar values reported in longitudinal studies on adults.[11] In work with adults there is no change in heat output due to growth; sigmas and coefficients of variation can be calculated immediately from the scatter of repeated serial measurements. Talbot, Wilson and Worcester [12] have concluded for adults that the "error of determination" as expressed by the coefficient of variation is in the neighborhood of 5 per cent. The analogous value of 9.10 per cent from this study of infants is impressively greater and

11. Benedict, F. G.: Am. J. Physiol. **110**:521, 1935. Blunt, K., and Dye, M.: J. Biol. Chem. **47**:69, 1921. Remington, R. E., and Culp, F. B.: Basal Metabolic Rate of Medical Students and Nurses in Training at Charleston, S. C., Arch. Int. Med. **47**:366 (March) 1931. Griffith, F. R., Jr.; Pucher, G. W.; Brownell, K. A.; Klein, J. D., and Carmer, M. E.: Am. J. Physiol. **87**:602, 1929.

12. Talbot, F. B.; Wilson, E. B., and Worcester, J.: Basal Metabolism of Girls: Physiologic Background and Application of Standards, Am. J. Dis. Child. **53**:273 (Jan., pt. 2) 1937. Talbot, F. B.: New England J. Med. **207**:318, 1932.

indicates that percentage fluctuations in heat production are relatively large during infancy. The effect of age on these recorded variations is further exemplified by dividing the observations in this study into two groups, those made before and those made after the age of 400 days. The data from all 4 infants show a value of $V_{diff.}$ of 10.4 per cent (71 degrees of freedom) before the age of 400 days and for the 3 infants with observations after 400 days a corresponding value of 7.6 per cent (50 degrees of freedom). The same data reveal a $\sigma_{diff.}$ of 1.81 calories before 400 days and of 1.63 calories after 400 days; that is, the absolute accuracy of the determinations was slightly improved for the older infants, but the striking decrease in the coefficient of variation resulted chiefly from increase in the magnitude of total heat production.

The information yielded by the study of these day to day fluctuations is of course limited by the small number of infants who could be followed and does not provide an accurate assessment of average fluctuations to be expected in a large group of infants selected at random. It is pertinent, therefore, to inquire whether or not the fluctuations are of similar magnitude in all infants. The data recorded for the infants C. H. and A. C. suggest strongly that day to day variability is greater in some infants than in others. Thus, for infant A. C. the coefficient of variation, $V_{est.}$, with its standard error was 9.95 ± 0.70 per cent; for infant C. H. the $V_{est.}$ was 8.00 ± 0.54 per cent. The difference between these values with the standard error of the difference is 1.95 ± 0.88 per cent, and the ratio of the difference to its error is 2.2. The ratio indicates that the difference is reliable, although not highly so, at approximately the 3 per cent level of significance. The smaller degree of variability in infant C. H. is what might have been expected on the basis of temperament. She was the most placid infant in the group.

Finally, it is of interest to compare these estimates of longitudinal variability with the degree of scatter in cross-sectional analyses of heat production during infancy. From the biometric study of Levine and Marples [2a] based on the data of Benedict and Taylor [1] for infants from 2 months to 2 years of age, $V_{est.}$ may be calculated. This amounts to 14.9 per cent, a degree of fluctuation considerably greater than that for the 3 infants here observed, whether they are considered individually or collectively.

2. Which measure of growth is related most closely to the increase in heat production in the same subject?

The relationship between heat output and growth in the present study is expressed by the statistics presented in table 3 and visualized by the data in charts 3 to 13. In the table the intensity of association between caloric exchange and each of the measures of growth is given first in terms of r, the correlation coefficient. The statistic is useful because the

standard error, or sigma, of r can be computed and used to determine whether or not the association is significant. However, in the form in which the data are given, the r's for one child cannot be compared in magnitude with those for the others. The absolute magnitude of these

TABLE 3.—*Relationships Between Basal Heat Production and Various Measures of Growth* *

Measure of Heat, y	Measure of Growth	Correlation Coefficient and Standard Error	Standard Error of Estimate σ est,y Calories	Coefficient of Variation V est. y per Cent
	C. H. ♀ 112 Observations			
Total calories	Age	0.842 ± 0.028	1.582	8.00
	Weight	0.844 ± 0.027	1.576	7.97
	Area	0.841 ± 0.030	1.592	8.06
	Height	0.781 ± 0.037	1.845	9.33
	Thickness	0.831 ± 0.030	1.642	8.31
Calories per Kg.	Age	−0.087 ± 0.094	0.181	7.89
	Weight	−0.261 ± 0.089	0.176	7.65
Calories per sq. m.	Age	0.336 ± 0.085	3.935	8.21
	Area	0.334 ± 0.085	3.944	8.23
Calories per cm.	Age	0.609 ± 0.060	0.023	8.86
	Height	0.624 ± 0.058	0.023	8.86
	A. C. ♂ 105 Observations			
Total calories	Age	0.815 ± 0.033	1.860	9.96
	Weight	0.834 ± 0.030	1.777	9.50
	Area	0.820 ± 0.032	1.840	9.86
	Height	0.810 ± 0.034	1.887	10.09
	Thickness	0.814 ± 0.033	1.868	10.00
Calories per Kg.	Age	0.194 ± 0.095	0.209	10.04
	Weight	0.199 ± 0.095	0.208	10.02
Calories per sq. m.	Age	0.286 ± 0.090	4.742	10.61
	Area	0.373 ± 0.085	4.603	10.30
Calories per cm.	Age	0.614 ± 0.061	0.025	10.28
	Height	0.606 ± 0.062	0.025	10.28
	J. D. ♂ 32 Observations			
Total calories	Age	0.284 ± 0.168	2.181	11.45
	Weight	0.215 ± 0.174	2.216	11.53
	Area	0.216 ± 0.171	2.216	11.53
	Height	0.295 ± 0.171	2.160	11.39
	Thickness	0.100 ± 0.178	2.262	11.86
Calories per Kg.	Age	−0.020 ± 0.180	0.310	12.39
	Weight	−0.330 ± 0.162	0.290	11.54
Calories per sq. m.	Age	−0.144 ± 0.178	6.088	11.79
	Area	−0.247 ± 0.172	6.148	11.91
Calories per cm.	Age	−0.278 ± 0.169	0.029	10.87
	Height	−0.014 ± 0.021	0.035	12.79

*Formulas for calculating the correlation coefficient (r) are given in all textbooks on statistics. The standard error of r was computed as $(1 - r^2) \div \sqrt{N - 2}$. The formulas for obtaining the standard error of estimate and the coefficient of variation are given in the footnotes of table 2. The square meters of surface area of the body were computed from weight, W, and height, H, by the widely used formula of DuBois: Area $= W^{0.425} \times H^{0.725} \times 71.84$. The calculation of body thickness is explained in footnote 6.

correlation coefficients is determined chiefly by the range in size of the subjects; that is, they are more a measure of growth than of intensity of association. In any single infant growth is constant, and the several r's relating to different measures of growth indicate relative intensity of association. The low coefficients yielded by infant J. D. do not in them-

selves mean that the associations were less intense with him than with the infants C. H. and A. C. They are chiefly an expression of the fact that observations on J. D. were continued over only six months, whereas

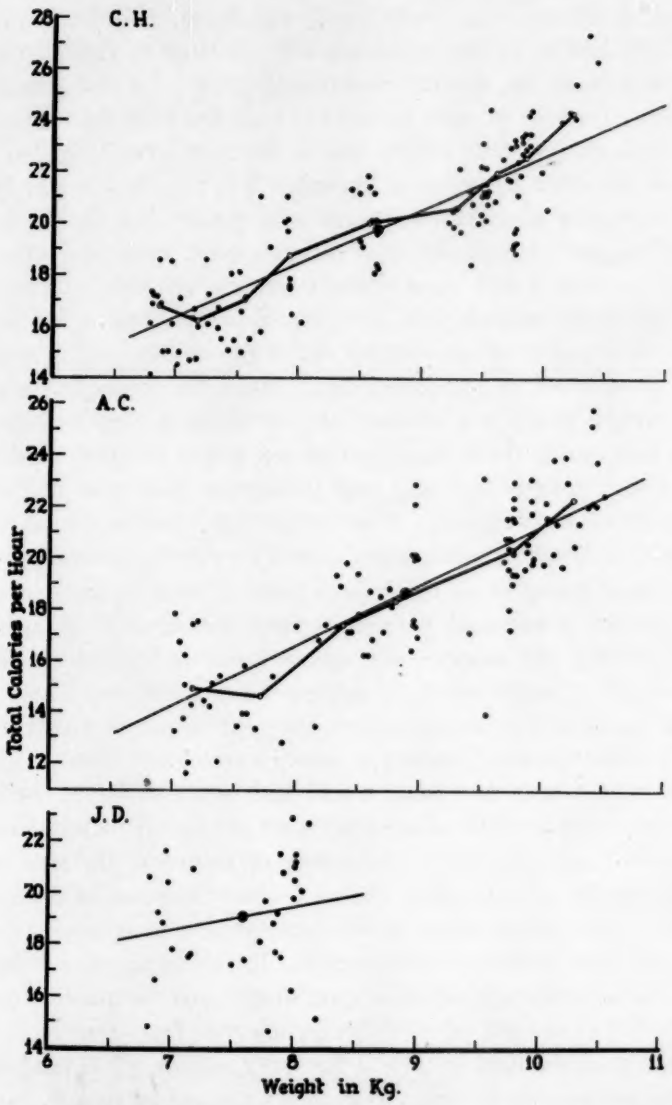

Chart 4.—Longitudinal observations on 3 infants showing the association between heat production and body weight.

the other 2 infants were studied for approximately fourteen months. The comparative data make clear the importance of a long period of observation, not only in assessing the significance of such associations but in

establishing the relative order of intensity of association for the several measures of growth. Thus, the correlation coefficients relating total calories per hour to age, weight, area, height and thickness for infant J. D. do not differ significantly from zero; for the other 2 infants these same relationships are statistically highly significant. But even with the infants C. H. and A. C. the errors are still too large to yield significant differences between the several measures of growth for the same child. Nevertheless, for both of these infants the r obtained for the relationship between total calories and weight was at least numerically higher than for any of the other measures of growth. The fact that it was higher than the r relating total calories to age is of greater significance than is immediately apparent from the small differences between the coefficients. Reference to table 1 will show that the path of growth in weight, as recorded by single weighings on the days of observation, is not smooth but rather is attended by considerable day to day fluctuation; in contrast, no error is involved in measuring age. Since the erratic variation in recorded weight would tend to lower the correlations, there is additional reason to believe that the association between weight and heat production is greater than between age and heat production even over the limited age range of fourteen months. Over longer age spans it is clear that a high degree of linear correlation with energy exchange cannot exist.

The second group of correlations in table 3, namely, those in which associations are determined between several measures of growth and calories per kilogram, calories per square meter of surface or calories per centimeter of height, are to be interpreted in a different way. Here the major purpose is to learn whether the heat output of a unit of size of the individual remains constant or shows a systematic trend as growth proceeds. The lack of any trend would lead to a correlation coefficient of zero; for example, if the calories per hour per square meter of surface area remained constant within the errors of recording throughout the period of growth, and therefore during a steady increase in the surface area of the body, there would be no demonstrable association ($r = 0$) between unit heat production and growth. In this group of correlations, then, low rather than high values of r are sought, and the question may be asked whether or not the values differ significantly from zero.

Inspection of the data in table 3 for the 2 infants, C. H. and A. C., with prolonged periods of observation shows that the correlation between calories per unit of height and total height is clearly greater than zero. The positive sign attached to the coefficient indicates that each added centimeter of height as growth proceeds is associated with an increased average number of calories per centimeter. The implication is strong that heat production is not related closely to this linear measure of growth. Similarly, for the relation between calories per unit of surface

area and total area of the body, the combined evidence from the correlation coefficients of the 2 infants indicates an association which differs significantly from zero. However, for the association between calories

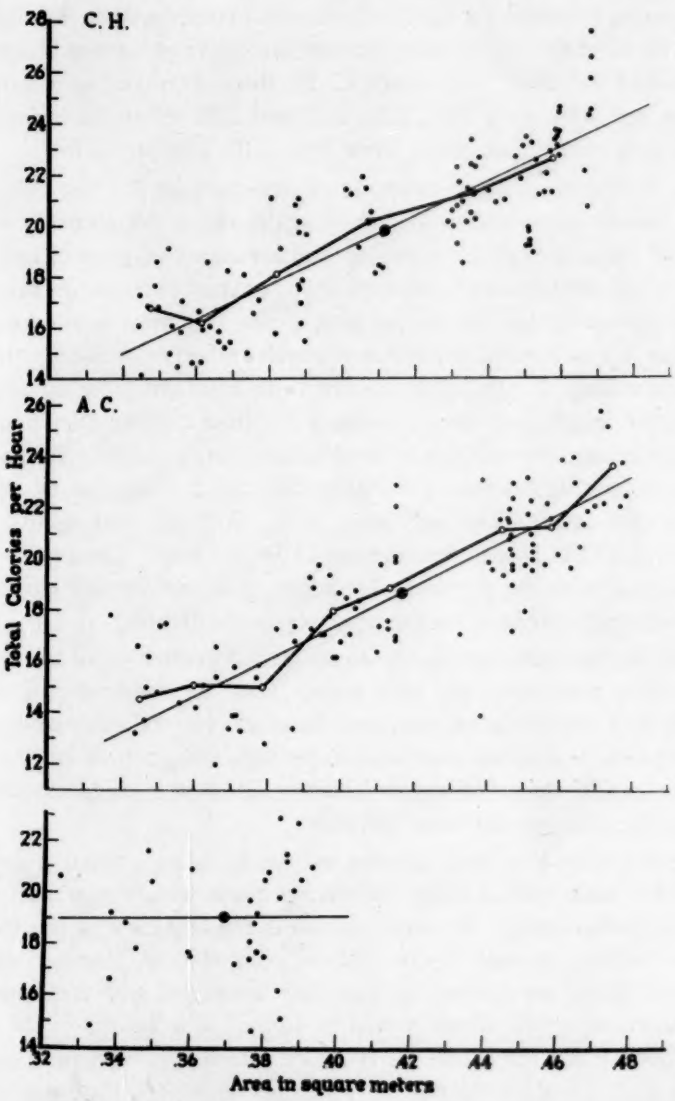

Chart 5.—Longitudinal observations on 3 infants showing the relation between heat production and surface area of the body.

per unit of weight and total body weight, infant C. H. yielded an r of -0.26 while infant A. C. gave an r of $+0.20$. The two r's are extremely low and considered together do not disclose significant evidence of devia-

tion from zero. Thus, although it is known from other studies that the heat production per unit of mass is distinctly less in the adult than in the infant, the data from this study do not disclose a significant change during the age period between 6 and 20 months. The situation can be visualized by computing averages for the 2 infants under consideration, each average embracing all of the observations during successive periods of about three and one-half months. For infant C. H. these averages in calories per kilogram per hour were 2.31, 2.35, 2.23 and 2.28. For the infant A. C. the averages in the same units were 2.01, 2.10, 2.08 and 2.16.

The data concerning coefficients of variation in the last column of table 3 permit immediate comparative appraisal of the accuracy of prediction of basal energy from the several measures of growth and independently of whether total calories are estimated directly or calculated after prediction of the calories per unit of size. In view of the foregoing discussion it is of particular interest to inquire whether or not a significant gain in accuracy of prediction results from estimating the calories per kilogram of weight and then computing the total calories over that to be derived from direct prediction of total calories from weight. In the order mentioned, the coefficients of variation for the 3 infants show: C. H., 7.97 per cent against 7.65 per cent; A. C., 9.50 per cent against 10.02 per cent; J. D., 11.53 per cent against 11.54 per cent. The result, which is in keeping with the previous discussion, does not furnish evidence of any substantial difference in the accuracy of prediction.

It will be profitable to examine in somewhat greater detail this relation between heat production and body mass. How accurately during the age period under consideration can total basal calories be estimated on the assumption of a constant heat output by each kilogram of body tissue? To what extent does the figure which expresses average calories per kilogram vary among different children?

The calculation of total calories on the basis of a fixed number of calories for each unit of body mass is the most widely practiced of the methods of estimation. In order to assess the accuracy of the method, the observations on each of the infants, computed as calories per kilogram per hour, were used to calculate averages and coefficients of variation covering the whole period of study. The results of the calculation follow: for the infant C. H., 2.29 calories $\pm$ 8.28 per cent; for the infant A. C., 2.09 calories $\pm$ 10.50 per cent; for the infant J. D., 2.52 calories $\pm$ 12.30 per cent, and for the infant J. S., 2.10 calories $\pm$ 8.95 per cent. The errors of prediction are slightly, not significantly, greater than those based on regression equations and listed in table 3. From the discussion in the preceding section it is clear that the bulk of the error arises from the random day to day fluctuations in recorded heat production and not from failure of the measure of growth to follow the changes in output energy.

The specific values, given in the preceding paragraph, for average calories per kilogram per hour for each of the 4 infants show considerable variability and suggest that this value is not the same for all infants.

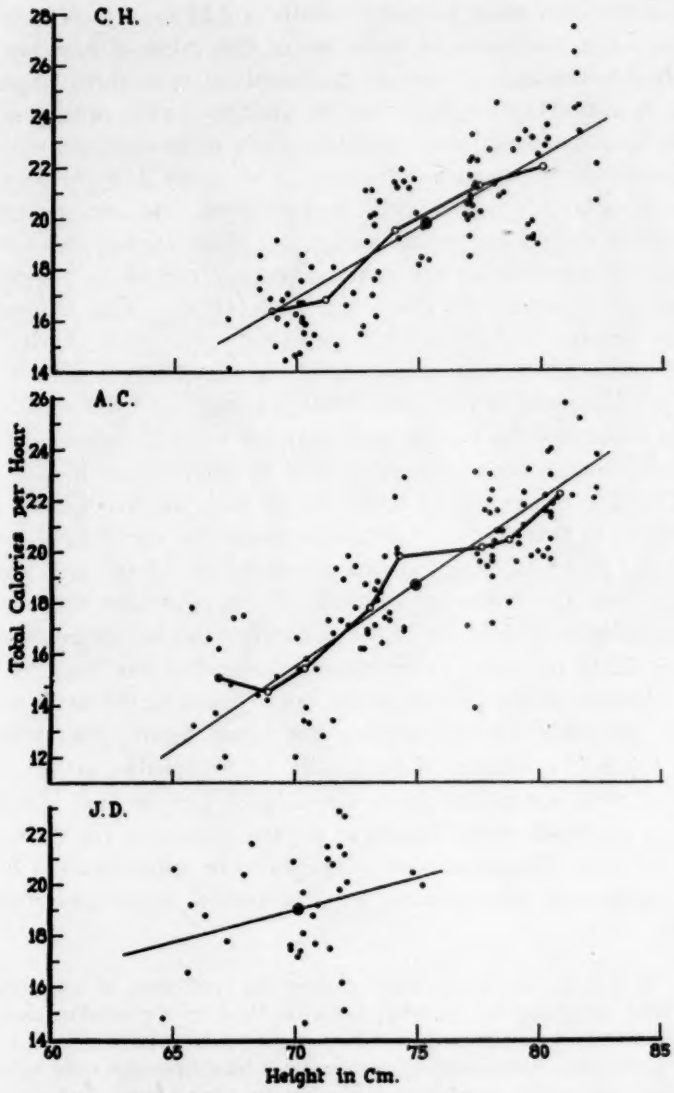

Chart 6.—Longitudinal observations on 3 infants showing the relation between heat production and height or length of the infants.

By application of "Student's" t test it can be shown, with one exception, that all possible differences between the values for each pair of infants are statistically highly significant. The exception concerns the difference

between the infants A. C. and J. S.; these infants exhibited practically the same average basal heat production per kilogram. The scatter among different infants with respect to basal heat production per kilogram would appear from this small group of 4 infants to be large. The average unweighted value for the 4 infants is 2.25 calories per kilogram per hour. The coefficient of variation of the value is 8.98 per cent. Although this estimate of variability, based on only three degrees of freedom, is extremely rough, it can be used to obtain an approximate figure for total cross-sectional variability likely to be encountered among isolated observations on many children. The figure 8.98 per cent is an estimate of variability between different children. An average estimate of variability within the child, that is, of fluctuations found during repeated measurements on the same child, is obtained by averaging [13] the coefficients previously given for each child. This estimate of variability within children is 10.32 per cent. The total variability of single observations on any infant about the mean for all infants, 2.25 calories per kilogram, is therefore 13.69 per cent ($\sqrt{8.98^2 + 10.32^2}$). The data assembled by Levine and Marples for 137 infants disclosed an over-all average heat production of 2.29 calories per kilogram per hour. The figure happens to agree closely with the average value for the 4 infants in this study. Variability about the mean figure cannot be calculated precisely from the data presented by Levine and Marples. However, from the errors of estimate of the equations relating total calories to weight an estimate of the variability can be computed. This estimate is 12.15 per cent. The figure is somewhat less than the 13.69 per cent obtained in the present study, but, in view of the small number of infants available for determining the latter figure, the agreement between the two estimates of variability is remarkably good. If the estimate of total variability from the data of Levine and Marples is accepted as the more nearly correct of the two estimates, then variability between different children can be computed to be approximately 6.5 per cent by subtracting the estimate for longitudinal variability found in this study.

13. In the first section of this paper sigmas and coefficients of variation were averaged after weighting the statistics for each child by the number of degrees of freedom used in determining them. Such averages are more stable, i. e., have a smaller error, than those obtained in any other way from the same volume of data. The results are useful when several averages made by the same technic are to be compared with each other. They do not, however, describe average variability with quantitative accuracy, since the figures are weighted heavily by the observations on the children who by chance happened to be studied the greatest number of times. In the present set of comparisons the estimates of variability for the four infants were averaged without weighting: $V_{av.} = \sqrt{\frac{\Sigma V^2}{4}}$.

Clagett and Hathaway [3] have recently reported 54 observations of basal heat production on 8 infants covering the growth period from 3 to 15 months. These authors likewise found that "for individual infants

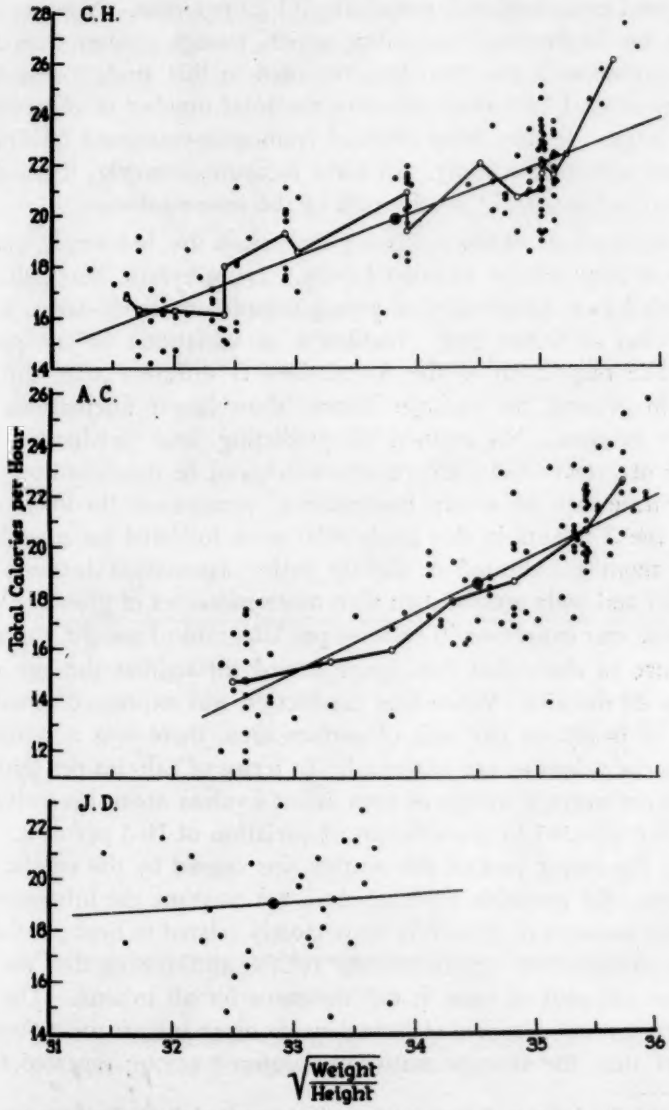

Chart 7.—Longitudinal observations on 3 infants showing the relation between heat production and body thickness. Body thickness is expressed by the square root of weight divided by height.

the values for calories per kilogram were relatively constant throughout the series of observations." The unweighted mean for the 8 infants

was 2.42 ± 0.238 (standard deviation) calories per kilogram per hour. Their data likewise permit estimation of the components of variability. The estimation of these coefficients of variation discloses: longitudinal variability, 5.54 per cent; variability between different infants, 9.84 per cent [14]; total cross-sectional variability, 11.29 per cent. Noteworthy is the value for longitudinal variability, which, though greater than 5 per cent, is considerably less than that recorded in this study. The lower value may in part be fortuitous, since the total number of observations was not large. It may have resulted from temperamental qualities of the infants selected for study. In some measure, however, it should be ascribed to technical skill on the part of the investigators.

The implications of the foregoing discussion are important, and for this reason they will be restated briefly. Daily erratic fluctuations in the recorded heat production of young infants are fairly large, in the neighborhood of 9 per cent (coefficient of variation) in the present study. The magnitude of the fluctuations is different with different infants; in general, the younger infants show larger fluctuations than the older infants. No method of predicting heat production from measures of growth can yield results which can be demonstrated to be more accurate than the erratic fluctuations. Analysis of the longitudinal data for the 2 infants in this study who were followed for a period of fourteen months indicated a slightly better association between heat production and body weight than with other measures of growth. When heat output was expressed in calories per kilogram of weight, there was no evidence to show that this figure varied throughout the age range from 6 to 20 months. When heat production was expressed in calories per unit of height or per unit of surface area, there was a significant change in the values as age advanced. In terms of calories per kilogram of weight the average scatter of each infant's values about his own mean value was expressed by a coefficient of variation of 10.3 per cent. It is clear that the major part of this scatter was caused by the erratic daily fluctuations; the available evidence does not warrant the inference that some other measure of growth is more closely related to heat production. It was shown further by statistically reliable differences that the heat production per unit of mass is not the same for all infants. The total variability in cross-sectional observations on many infants must therefore be greater than the average scatter encountered among repeated obser-

14. Variability between different infants is determined from the averages of all observations on each of the infants. Since most of the averages in the data of Clagett and Hathaway were determined from only 4 or 5 observations, they possess an appreciable standard error. Because these standard errors were known, the appropriate correction was applied before the average variability between different infants was computed.

vations on the same infant. Total variability, with a range of values from this and from other studies of between 11.3 and 13.7 per cent, is made up of two components: variability among different infants, with a value between 6.5 and 9.8 per cent, and longitudinal variability in the individual infant, with a value between 5.5 and 10.3 per cent. An

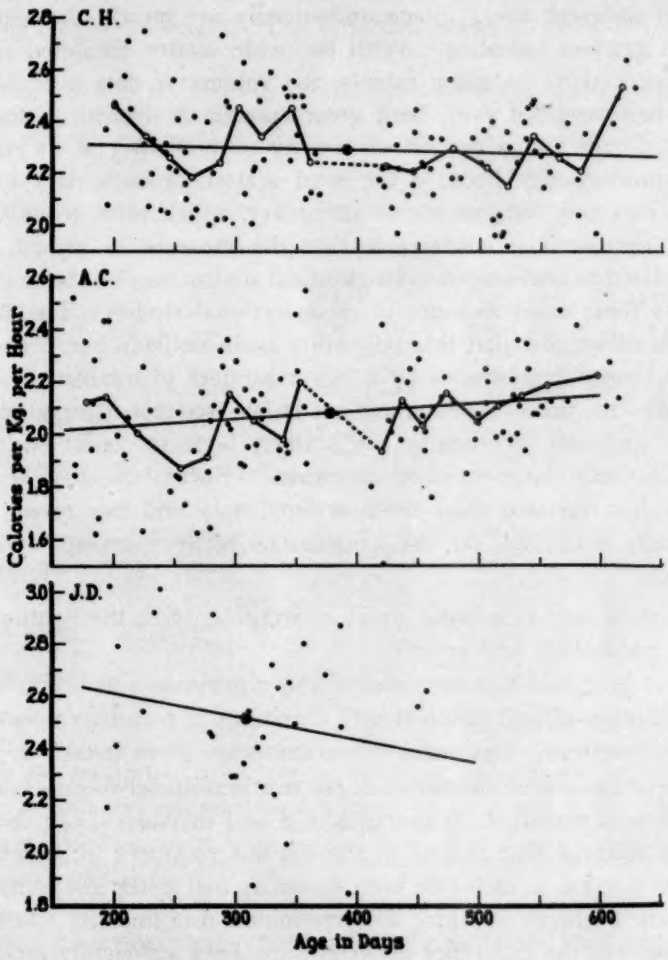

Chart 8.—Longitudinal observations on 3 infants showing the relation between heat production per unit of body mass and age.

appreciation of the magnitude of these components of variability is essential to an understanding of what accuracy can be hoped for in predicting heat production from measures of growth.

There is no unanimity of opinion recorded in the literature regarding the most suitable measure of growth for predicting metabolism.

Weight,[15] height [2a, b] and surface area [16] have each in various studies been found to parallel heat production most closely. A completely satisfying explanation of the discrepancies cannot be given. Some discrepancies undoubtedly result from differences in the age periods embraced by the observations. Some may be associated with the technical problem of maintaining comparable standard conditions for infants of different ages. Some undoubtedly are merely the result of errors of random sampling. With the wide scatter exhibited among single observations on many infants, the volume of data available for analysis has rarely, if ever, been great enough to determine that one measure of growth has certain superiority over another in its relation to heat production. Because the total scatter of such data can be resolved into two components of variability, which arise from wholly different causes, it is conceivable that the measure of growth most closely related to heat output in longitudinal studies may not be so closely related as some other measure in cross-sectional studies. The limited data at hand suggest that this possibility is an unlikely one. There is need for longitudinal studies on a larger number of infants. Even in such studies the uncontrolled errors are large; frequent observations are desirable, and one investigator can scarcely hope to collect such data for a sufficiently large number of infants. Such data, however, are distinctly less variable than cross-sectional data and can reveal more convincingly than they can the associations between growth and heat production.

3. Is there any systematic trend or irregularity in the relationships between metabolism and growth?

It may be noted that analyses of the observations failed to reveal any relationship of heat production to variations in season or in environmental temperature. Dates and temperatures are given in table 1.

Material bearing on the nature of the relationship between metabolism and growth is presented in charts 3 to 8 and in table 4. In the spot diagrams relating heat output to the various measures of growth the regression line has in each case been shown as well as the line connecting the periodic averages on which the determination of linearity was based. In no case was the difference between these lines sufficiently great that statistical departure from linearity could be established. So far as general trends are concerned (i. e., rectilinearity or curvilinearity of the regression) this result is not surprising. The age span was short, and slight degrees of curvature would be difficult to demonstrate.

These observations are of interest because of the impression that a definite irregularity in metabolic rate relative to growth characterizes

15. Footnotes 2 *b* and 12.

16. Footnotes 1 and 2 *a*.

the period immediately following the first year of life. For example, the curve expressing the data of Benedict and Talbot [1] in terms of calories per kilogram referred to age shows a definite curvature at this point, forming the crest of a sharp peak. For the same data a second relationship was shown by Adams and Poulton [2b] to indicate another slight irregularity. These authors noted a "kink" in the curve relating carbon dioxide output to weight. The inflection began at about a year of age

TABLE 4.—*Tests for Linearity of Regression for the Relationships Between Calories and the Various Measures of Growth* *

Measure of Heat	Measure of Growth	Correlation Coefficient and Standard Error	Correlation Ratio and Standard Error	$\frac{\zeta}{\sigma\zeta}$	ζN	Linearity of Regression
	C. H. ♀ 112 Observations					
Total calories	Age	0.843 ± 0.028	0.843 ± 0.028	0	0	Linear
	Weight	0.844 ± 0.027	0.910 ± 0.016	1.8	13.2	Linear
	Area	0.841 ± 0.030	0.828 ± 0.030	0	0	Linear
	Height	0.781 ± 0.037	0.822 ± 0.031	1.4	6.5	Linear
	Thickness	0.831 ± 0.030	0.880 ± 0.022	0.7	9.5	Linear
Calories per Kg.	Age	−0.087 ± 0.094	−0.139 ± 0.078	0.5	1.3	Linear
	Weight	−0.261 ± 0.094	−0.148 ± 0.093	0	0	Linear
Calories per sq. m.	Age	0.336 ± 0.085	0.485 ± 0.072	1.8	13.7	Linear
	Area	0.334 ± 0.085	0.470 ± 0.074	1.7	12.2	Linear
Calories per cm.	Age	0.609 ± 0.060	0.700 ± 0.050	1.9	13.3	Linear
	Height	0.624 ± 0.058	0.682 ± 0.051	1.2	5.7	Linear
	A. C. ♂ 105 Observations					
Total calories	Age	0.815 ± 0.033	0.827 ± 0.031	0.9	2.1	Linear
	Weight	0.834 ± 0.030	0.873 ± 0.023	1.3	6.5	Linear
	Area	0.820 ± 0.032	0.827 ± 0.031	0.5	0.7	Linear
	Height	0.810 ± 0.034	0.811 ± 0.034	0.3	0.3	Linear
	Thickness	0.814 ± 0.033	0.823 ± 0.032	1.5	1.0	Linear
Calories per Kg.	Age	0.194 ± 0.095	0.278 ± 0.091	1.4	3.9	Linear
	Weight	0.199 ± 0.095	0.189 ± 0.095	0	0	Linear
Calories per sq. m.	Age	0.286 ± 0.090	0.455 ± 0.078	1.8	13.2	Linear
	Area	0.373 ± 0.085	0.459 ± 0.078	1.4	7.2	Linear
Calories per cm.	Age	0.614 ± 0.061	0.623 ± 0.060	0.5	1.1	Linear
	Height	0.606 ± 0.062	0.634 ± 0.059	1.0	3.4	Linear

*The formulas involved in the tests for linearity of regression and the symbols in the table are those given by Garrett.[10] Both tests suggested by Garrett were applied to the data; that is, to demonstrate that regression is nonlinear (1) the ratio of ζ to its standard error should be greater than 2 and preferably greater than 3, or (2) the product of ζ and the number of observations should be greater than 11.37. The combined evidence from the two tests and from the 2 infants does not disclose significant departure from linearity of regression in any of the relationships.

and was somewhat exaggerated when the variables were expressed in terms of their logarithms. In the present study, as has been stated, no irregularities were found in the curves relating calories per kilogram to age which could not be explained on the basis of the daily fluctuations in metabolism of the subjects. Nor could evidence be obtained for the presence of a "kink" in the curves describing the relationship studied by Adams and Poulton (chart 14).

In view of these differences in results it seemed possible that the apparent irregularities in the curves of Benedict and Talbot might

similarly have fallen within the wider scatter of the cross-sectional data which they represented. Indeed, these authors themselves, in describing the peak in the curve relating calories per kilogram to age, stated that "the striking scatter of all of these points makes it extremely difficult

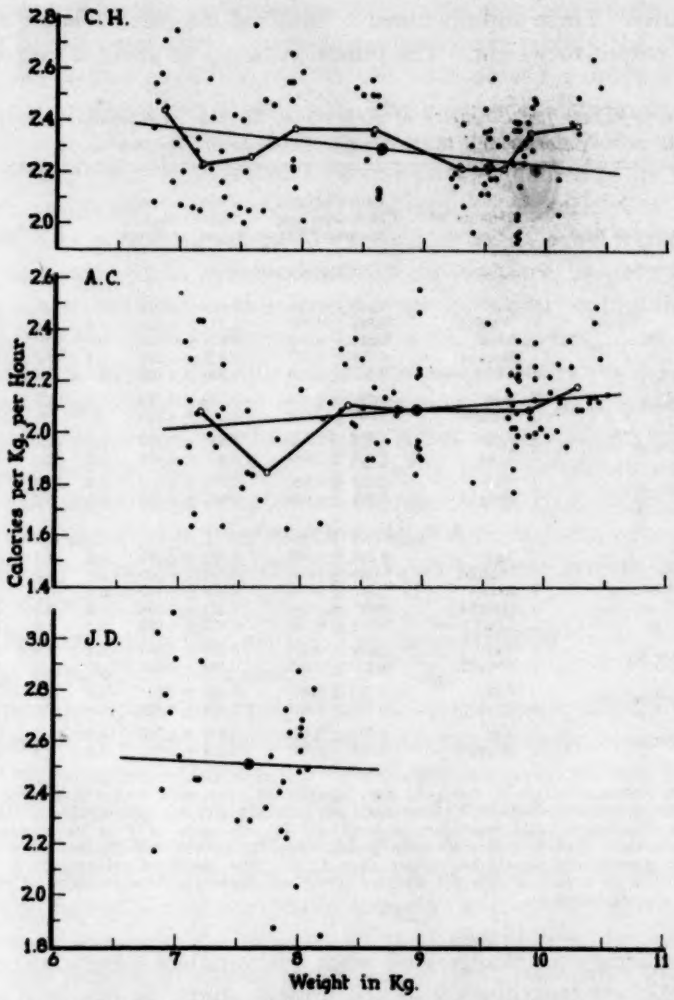

Chart 9.—Longitudinal observations on 3 infants showing the relation between heat production per unit of body mass and body weight.

to lay on anything in the nature of a smoothed curve that could be considered justifiable." A mathematical analysis of the data of Benedict and Talbot to determine whether or not the peaks in their curves were statistically reliable seems unnecessary in view of the fact that two subsequent studies are now available covering at least part of the age period

in question. In both, probably because of improved methods, the scatter is less than in the earlier work of Benedict and Talbot. In neither is there any evidence of metabolic irregularities causing a peak in the curve of calories per kilogram referred to age.

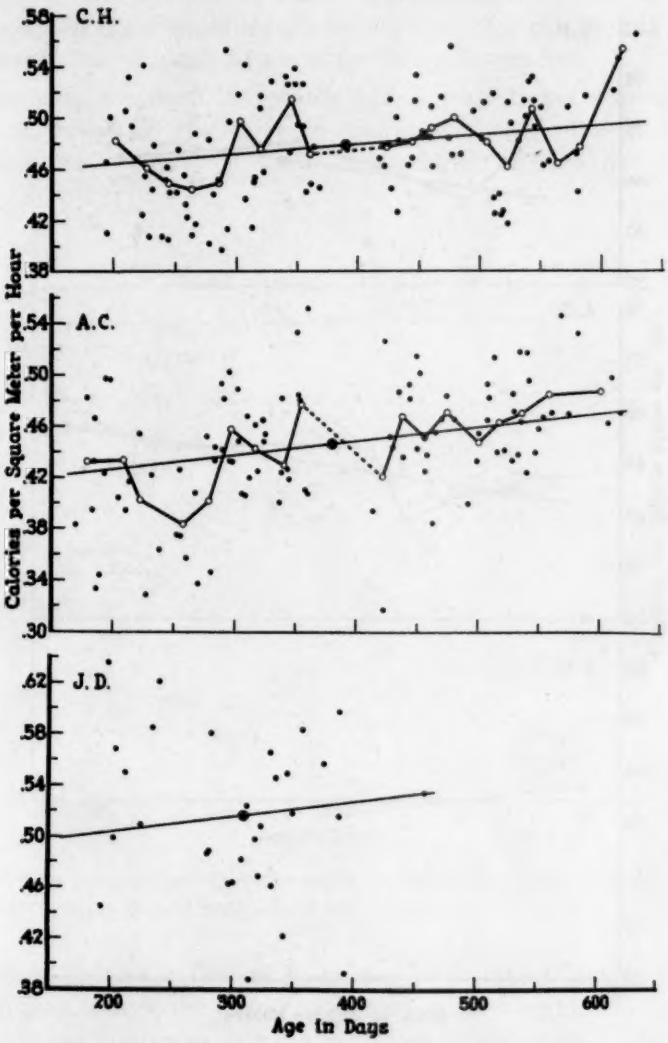

Chart 10.—Longitudinal observations on 3 infants showing the relation between heat production per unit of body surface and age.

One of these investigations has already been discussed, namely, that of Clagett and Hathaway [3] dealing with longitudinal observations on 8 infants between 3 and 15 months of age. Heat production per unit of mass remained roughly constant throughout the age span. The average

unweighted value for the 8 infants was 2.42 ± 0.238 (standard deviation) calories per kilogram per hour. Statistically this result does not differ from the average value of 2.25 ± 0.202 calories per kilogram per hour found in the present investigation.

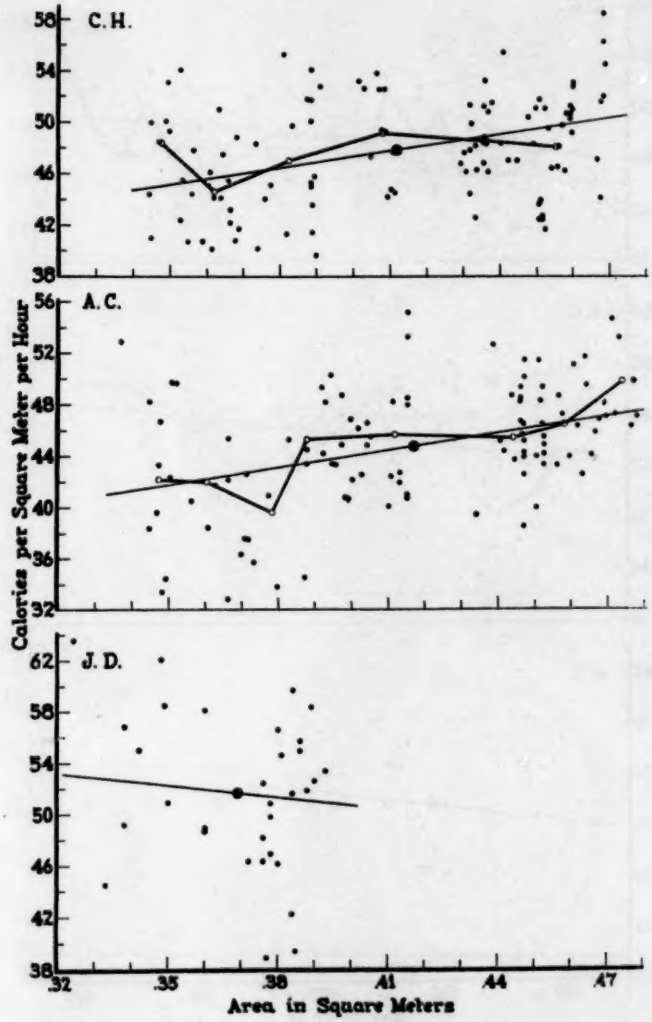

Chart 11.—Longitudinal observations on 3 infants showing the relation between heat production per unit of body surface and the total surface area of the body.

The second investigation is the extensive and exceedingly painstaking cross-sectional analysis of longitudinal observations collected at the Child Research Council in Denver and reported by Lewis, Kinsman and Iliff.[6] These data deal with children after the age of 2 years. They

thus do not cover the period involving the crest of the peak in the curves of Benedict and Talbot, but they do extend over the greater part of the portion involving the downward bend up to the age of 5 years. The trend of calories per kilogram is charted by them from periodic averages between the ages of 2 and 12 years. These trend lines (one for each of the sexes) do not disclose significant evidence of a change in a gradual downward slope throughout the entire age span studied.

The period between 20 months and 2 years is not represented in either of these two studies or in the present one. But if the lines enclosing the scattered points [17] representing calories per kilogram

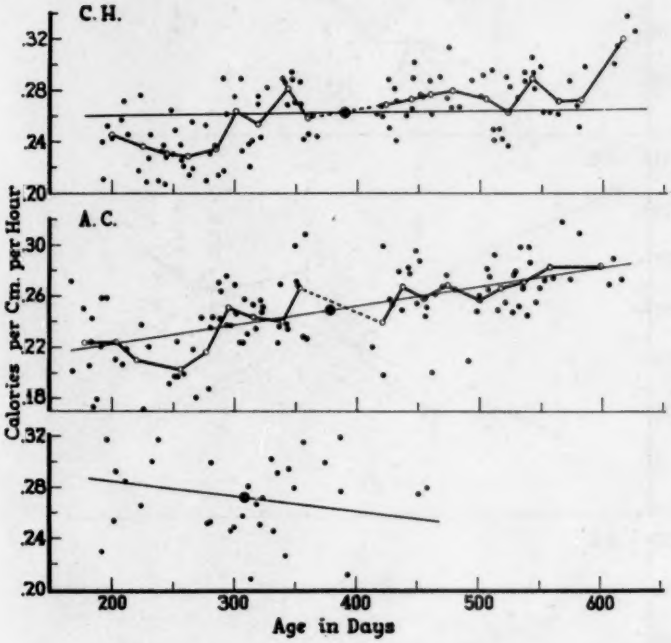

Chart 12.—Longitudinal observations on 3 infants showing the relation between heat production per unit of body height and age.

referred to age in the Denver report are extrapolated back to the time of birth they include the curves representing the longitudinal data both of Clagett and Hathaway and of the present investigation. The Denver data for boys show a mean value of 2.30 calories per hour per kilogram at the age 2 to 3 years and decline to a mean value of 1.41 calories per kilogram per hour at the age 12 to 13 years; for girls the data show values of 2.25 and 1.39 calories per kilogram per hour corresponding

17. The area enclosed between the parallel lines representing the average plus and the average minus two standard deviations.

respectively to the ages 2 to 3 years and 10 to 11 years. The downward slope of the lines naturally suggests that a similar slope may obtain for younger infants. The data in this investigation do not oppose such an

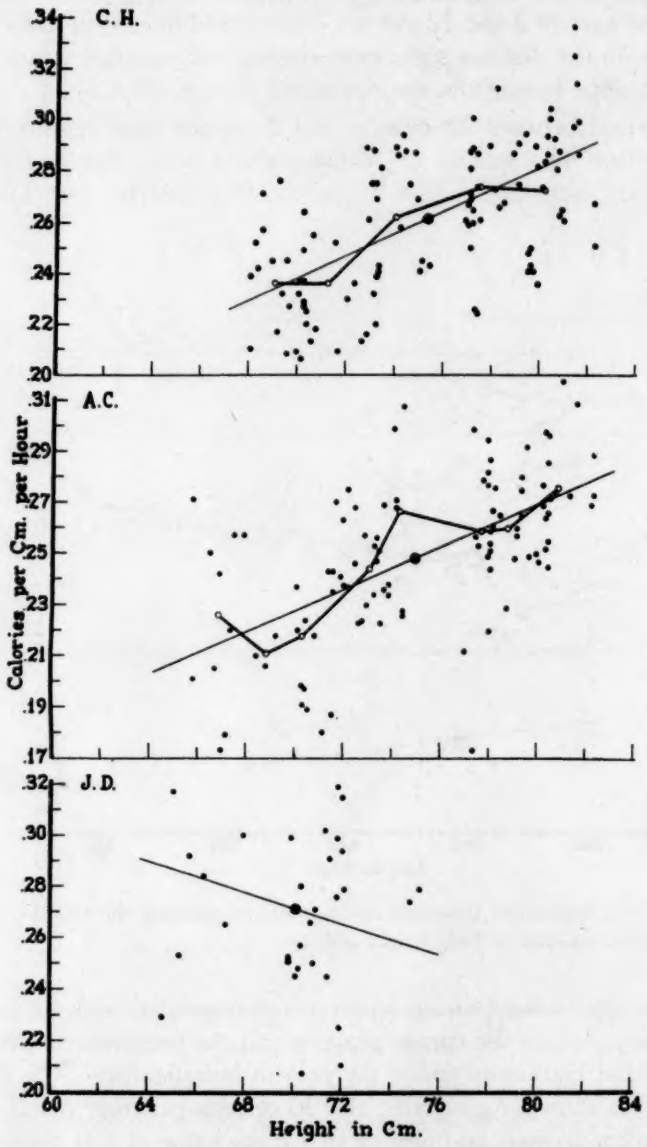

Chart 13.—Longitudinal observations on 3 infants showing the relation between heat production per unit of body height and height of the body.

inference. In fact, if the correlation coefficient relating calories per kilogram to weight for infant C. H. had been considered independently

of the data for infant A. C., its value, -0.261 ± 0.089, would have been interpreted as significant. The negative sign before the coefficient implies a downward slope of the regression line. However, the combined evidence from both infants and from correlations with both age and weight does not provide acceptable proof of such a downward slope.

Because the combined data from the three studies do not disclose evidence of an appreciable irregularity or peak in metabolic rate (calories per kilogram) in the period following the first year of life and

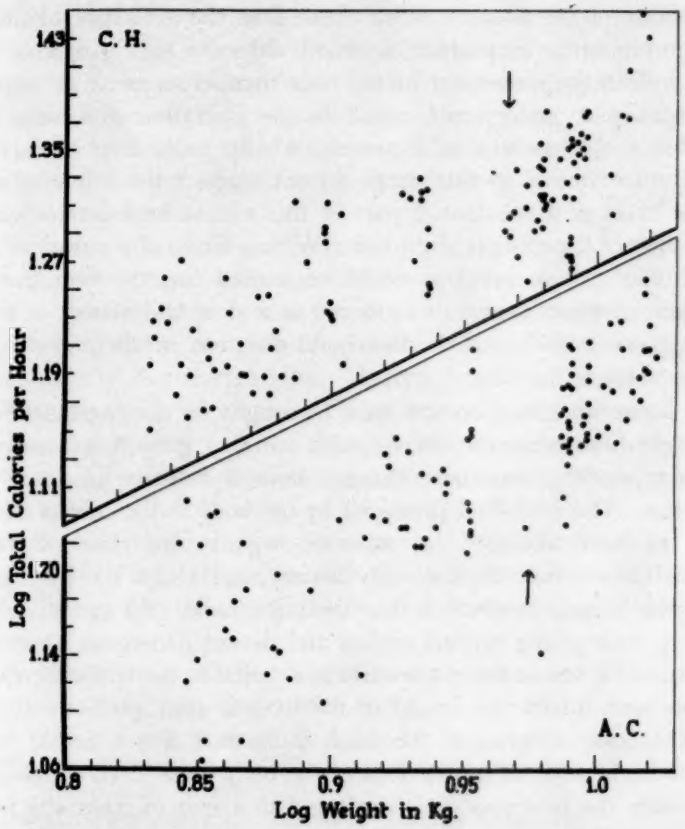

Chart 14.—The logarithm of calories per hour referred to the logarithm of body weight for infants C. H. and A. C. The arrows indicate the time when walking began. (In the work of Adams and Poulton heat production was represented by the logarithm of carbon dioxide output. The authors stated, however, that the infection which they noted was present also when the curves were constructed as in this chart, with heat output represented in terms of calories. Reference to table 1 indicates that after the beginning of walking there was no systematic reduction in the respiratory quotient. If such a reduction had been present, it would have supported the hypothesis of Adams and Poulton that this period is associated with a shift from fat storage to fat utilization.)

also because the values of Benedict and Talbot were too widely dispersed to beget confidence in the accuracy of any trend line drawn through them, it appears unlikely that any irregularity exists.

Largely on the basis of the parallelism between the supposed rapid fall in metabolic rate between the ages of 1 and 3 years and the concurrent rapid decline in the rate of weight gain, the theory has been advanced [2c] that the excess heat production per kilogram of tissue during infancy and childhood is "produced by and due to growth." It is certain that some energy must be utilized to bring about the "motion of growth." The synthesis of compounds which enter into the structure of newly formed protoplasm, the pushing aside of old cells to make room for new and indeed the movement of the cells themselves must all require an expenditure of energy and result in the liberation of heat. The magnitude of this moiety is, however, wholly unknown. The data collected and reviewed in this paper do not support the inference that the whole or even a substantial part of this excess heat production is an expression of the motion of growth. Within limits of accuracy which are admittedly not so great as could be wished for, the reduction in calories per kilogram appears to proceed at a slow and almost uniform rate throughout infancy and childhood and does not parallel the changes which characterize the rate of growth.

Since some other explanation must be sought for the high metabolic rate of the infant, it is relevant to point out that growth is associated with many possibly important changes besides increase in mass and surface area. The total heat produced by the body is the sum of all the fractions of heat liberated by separate organs and tissues. It is reasonably certain that metabolically active organs like the liver have a higher rate of heat production than resting muscle. As age advances, the relative mass of the various organs and tissues undergoes important alterations. The size of the extremities in relation to the trunk increases. In the newborn infant the weight of the liver is approximately 10 per cent of the body weight; in the adult it is only 5 per cent. Such alterations in the relative proportions of the body must to an appreciable extent modify the heat production referred to a unit of mass and independent of its composition.

SUMMARY AND CONCLUSIONS

Longitudinal observations of basal heat production are reported for 4 infants between the ages of 6 and 20 months. There were a total of 217 observations, covering the entire age span, on 2 of the infants. Forty additional observations on 2 other infants covered shorter periods.

An appraisal is given in statistical terms of the day to day fluctuations in the basal heat production of individual infants. The magnitude of

these fluctuations is large. Expressed in terms of the coefficient of variation they amount to 9 per cent in this study, as compared with a reported value of 5 per cent for adults. Some infants show a greater degree of fluctuation than others, and in general the young infant is more variable than is the same infant at a later age.

The data are analyzed to determine the relation between heat production and several measures of growth. The association between total calories and body weight was closest. When heat production was referred to a unit of mass (calories per kilogram), there was no evidence of change with advancing age. In contrast, when heat production was referred to a unit of surface area or to a unit of height, there was reliable evidence of change with growth. These data do not deny the inference which might be drawn from extrapolating to younger infants the extensive data reported by Lewis, Kinsman and Iliff, namely, that heat production per kilogram of weight declines steadily throughout the years of childhood.

Different infants of the same age vary significantly in the quantity of heat produced per kilogram of body weight.

The demonstrable accuracy with which basal heat production can be predicted from measures of growth is limited by the magnitude of erratic day to day fluctuations. Over the age span studied, prediction on the assumption of a constant heat output per kilogram of weight is not significantly less accurate than prediction on the basis of regression equations. The total error of prediction covers a range in this study and in other reported studies of between 11.3 and 13.7 per cent. This error is composed of two components: variability among different infants, with values between 6.5 and 9.8 per cent, and longitudinal variability in the individual infant, with values between 5.5 and 10.3 per cent.

Evidence could not be adduced to support the view that the excess heat production per kilogram of tissue of the infant over that of the adult is due in any substantial degree to the normal changes in the rate of growth.

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DIABETIC COMA, ACUTE PANCREATITIS AND BACILLUS WELCHII PERITONITIS

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At the Children's Memorial Hospital from 1921 to 1942, postmortem examinations have been performed on 10 children who died during diabetic coma, 5 of whom showed complications (summarized in the table). Acute pancreatitis with peritonitis was found in only 1 patient, which represents an incidence of 10 per cent in this series. The complications in the other 4 were bronchitis, pneumonia, gastroenteritis and

Fatal Diabetic Coma According to Age of Subject and Complications

Subject	Age	Complication
1	15 mo.	None
2	2 yr.	None
3	3½ yr.	None
4	7 yr.	None
5	11 yr.	None
6	11 mo.	Gastroenteritis
7	4½ yr.	Pneumonia
8	4½ yr.	Bronchitis
9	10 yr.	Septicemia and laryngotracheitis
10	13 yr.	Pancreatitis and peritonitis

septicemia with laryngotracheitis. In 5 of the 10 patients the condition was uncomplicated and death was attributed to the severity of the diabetic coma. In a group of 26 cases with postmortem examinations, Root [1] found 4 instances of pancreatitis complicating diabetic coma, an incidence of 15 per cent in this group. Similarly, in the 4 cases in his group the pancreatitis was not recognized clinically, and the author stressed the point that the diagnosis of acute pancreatitis should be considered in any case of diabetic coma in which the condition of the patient is extreme and in which prompt recovery does not occur. Because of the unusual combination of acute pancreatitis and Bacillus welchii peritonitis in a patient with fatal diabetic coma and because the abdominal conditions had been considered consistent with those found in uncom-

From the Metabolic Clinic, The Children's Memorial Hospital.

1. Root, H. R.: Diabetic Coma and Acute Pancreatitis with Fatty Livers, J. A. M. A. **108**:777 (March 6) 1937.

plicated diabetes, it seemed worth while to report this case in detail and to discuss some of the difficulties in the differential diagnosis of the "abdominal syndrome" in diabetic coma.

REPORT OF A CASE

History.—A 13 year old white boy was admitted to the Children's Memorial Hospital in a comatose condition of twenty-four hours' duration. The history was extremely meager, since the patient was not living at home. He had had bronchial asthma for the preceding five years and for the last two years he had complained of intermittent abdominal cramps and constipation. For some time before his admission—the exact date was not available—the patient had had abnormal thirst and frequent urination. Three days before admission he complained of severe abdominal pain, vomiting and drowsiness.

On admission the patient presented a striking picture of coma, emaciation, dehydration and Kussmaul respirations. The skin and mucous membranes were dry, and there was a profuse distribution of hyperkeratotic papules over the extremities; deep excoriations were present at the angles of the mouth. The eyeballs were soft, and the conjunctivas were intensely injected. The chest appeared emphysematous; the pulmonary fields were clear. The heart tones were barely heard, and the blood pressure was 80 mm. systolic and 0 mm. diastolic. The abdomen was boardlike and did not appear distended. The edge of the liver extended to the level of the iliac crest. Many hard masses (fecal) were palpable throughout the abdomen. The extremities were emaciated, and there was no peripheral edema. The urine contained sugar (4 plus) and acetone. The results of the chemical studies of the blood were as follows: sugar content, 482 mg.; cholesterol content, 497 mg.; fat content, 5,200 mg. per hundred cubic centimeters; carbon dioxide-combining power, 27.4 volumes per cent.

Course in the Hospital.—The therapy consisted of continuous venoclysis with lactate Ringer (Hartmann's) solution and physiologic solution of sodium chloride; insulin was given immediately and then every hour for several hours. Because of the nature of the abdominal rigidity, surgical consultation was obtained, and the impression of the abdominal condition was that "the abdominal distention and rigidity were no indications for surgical intervention, rather that they were consistent with the abdominal syndrome seen in uncomplicated cases of diabetic coma." Because of the anuria and the low blood pressure, 100 cc. of 10 per cent solution of sodium chloride was administered intravenously. Shortly thereafter, the blood pressure rose to 116 mm. systolic and 72 mm. diastolic and the bladder yielded about 100 cc. of dark amber urine. The blood sugar content was 472 mg. per hundred cubic centimeters, and the urine still contained sugar (4 plus) and acetone. However, despite all measures the blood pressure dropped, the pulse became thready, Cheyne-Stokes respirations appeared and the patient did not respond. Death occurred about seventeen hours after the patient's admission to the hospital. The total amount of intravenously administered fluids was 3,000 cc., and the total dose of insulin was 220 units of regular insulin.

Gross Postmortem Examination.—When the skin and subcutaneous tissue were separated over the abdominal cavity, the muscle tissue was almost absent and there occurred a spontaneous rupture of the peritoneum by the pressure of gas within the peritoneal cavity. The stomach, colon and small intestine were enormously dilated and dark red with mottled areas of green and black. There was

about 300 cc. of reddish-stained, cloudy, foul-smelling fluid within the peritoneal cavity. There was a loose layer of fibrin over the loops of the small intestine and colon. Over the serosal surface of the intestine, particularly in the region of the ileum, there were small gas-containing blebs. The retroperitoneal tissue in both flanks was crepitant, and the peritoneum was raised into blebs. The appendix, except for the serosa, appeared normal. There were no perforations of the intestine.

The inferior margin of the liver extended to the iliac crest, and the anterior surface was covered by a thin layer of fibrin. The pleural cavities contained no free fluid. The pericardial cavity contained about 20 cc. of straw-colored fluid.

The lungs filled the entire pleural space. The posterior half of the lateral surface and the entire base of the lower lobe of the right lung were bound to the parietal pleura by dense fibrous adhesions. Both lungs were severely emphysematous. The trachea and bronchi were filled with thick greenish material which had both digested and stained the lining surface. Sections of the lungs showed this material filling the major part of the bronchial tree, and many small necrotic areas were noted on the cut surfaces.

The heart was of average weight. The pericardium was smooth, and the myocardium was flabby and pale brown-red. The atrioventicular, pulmonary and aortic orifices were normal. The coronary vessels revealed nothing unusual. The abdominal portion of the aorta showed atheromatous streaks on the intimal surface.

The liver weighed 1,250 Gm. The cut surfaces showed a honeycomb pattern of pale yellow and brown, and the lobular markings were accentuated. The gallbladder and adrenal glands appeared normal.

The pancreas weighed 30 Gm. There was no external evidence of necrosis, and the consistency was not unusual. On section through the head of the pancreas, the interstitial tissue appeared normal.

The kidneys were soft and together weighed 280 Gm. The capsule stripped with ease, and the surface was pale yellow studded with minute hemorrhages. On section, the cortex was wide and pale yellow; the medulla appeared darker, and the markings were indistinct. The pelves and ureters appeared normal. The urinary bladder was not unusual.

The esophagus contained the same greenish material which was present within the trachea and bronchi. The stomach was enormously distended with about 400 cc. of the same material; the wall was dark red. The entire ileum was dilated, and the vessels of the serosa appeared thrombosed. The mucosa was dark red and necrotic in places. Within these necrotic areas, the process had extended through the wall to the serosa, so that there remained this thin layer between the lumen of the intestine and the peritoneal cavity. Blebs of gas were also seen on the mucsoal and serosal surfaces, although they were more frequent on the latter. The appendix appeared normal. The colon was greatly distended with inspissated fecal material; at the hepatic flexure the diameter of the colon was approximately 6 inches (15 cm.).

Postmortem cultures from the heart blood and the peritoneal fluid showed gram-negative bacilli of the colon group and gram-positive anaerobic spore-bearing bacilli which belonged to the saccharolytic group. These anaerobic bacilli produced stormy fermentation in litmus milk after four days' incubation and gave a positive Welch-Nuttall reaction in a rabbit. The colonies in the shake tubes were rougher than the colonies of B. welchii. Because of the reaction in litmus milk and the

positive Welch-Nuttall reaction these organisms more closely resemble B. welchii. Complete identification was not possible without antiserums.

Microscopic Postmortem Examination.—Heart: The myocardial fibers were spread apart; the nuclei stained well, and the cells appeared normal. Staining for fat showed only a minimal amount of fine fat globules within the cells. Staining for glycogen revealed a few isolated fibers harboring small amounts of glycogen.

Lungs: Sections revealed various stages of emphysema. Many of the bronchioles contained necrotic debris, and the lining cells were missing. Isolated small necrotic areas were noted within the parenchyma of the lungs close to the bronchioles.

Liver: The hepatic cords were swollen, and the cells were distinctly vacuolated. This change was most pronounced at the periphery of the lobule of the liver. The central veins were distended, but the portal veins and bile ducts appeared normal. Staining for fat showed a moderate number of fat globules within the cells in the center of the lobule. Staining for glycogen showed large amounts of glycogen dispersed throughout the hepatic cords, chiefly within the periphery of the lobule. Many areas revealed glycogen within the nuclei of the cells, but that within the cytoplasm was more prominent.

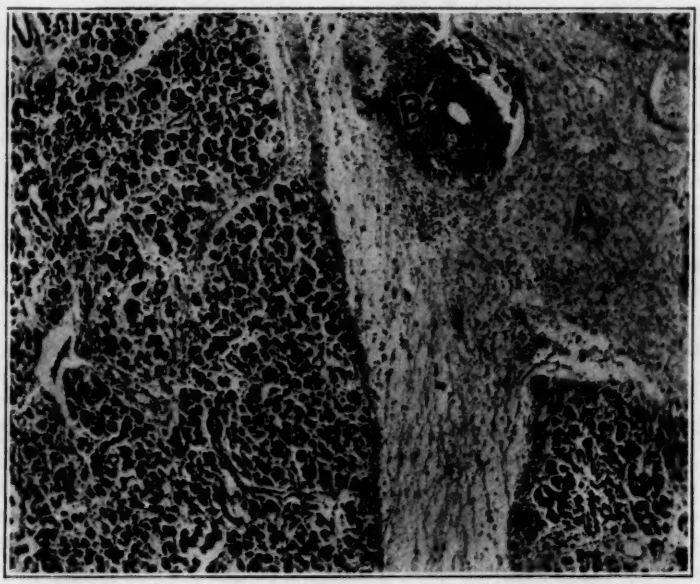
Pancreas: Sections from the head of the pancreas showed large areas replaced by pink-staining granular debris harboring many inflammatory cells, degenerated acinar cells and remnants of small and large ducts. The islets of Langerhans were similarly involved in the necrotic and inflammatory change, for none were recognizable in these sections. In places small islands of acinar tissue were widely separated by necrotic areas; many degenerated acinar cells were seen at the periphery; almost no islets of Langerhans were seen in these sections. Collections of inflammatory cells and cellular debris were visible within some of the small and large ducts, the walls of which were edematous and infiltrated with polymorphonuclear leukocytes. Several small areas of hemorrhage were noted. The blood vessels and capillaries were extremely engorged (shown in the accompanying photomicrograph). Sections from the tail showed this process to a less extreme degree; many of the lobules were fairly well preserved. The islets of Langerhans were few and far between; some showed lymphocytic infiltration, while in others many pyknotic nuclei were seen. Here also many of the small ducts contained granular debris and few inflammatory cells. Sections stained with Mallory's aniline blue showed little increase in the interacinar or interlobular connective tissue.

Spleen: The malpighian corpuscles were small and not well demarcated. The sinuses were engorged with red blood cells, and numerous pale-staining lipoid histiocytes were seen throughout.

Kidneys: The glomeruli were well stained and moderately distended; the cellular architecture was well preserved. The glomerular capillaries were engorged; the subcapsular spaces were clear, and Bowman's capsules were intact. The tubular structure showed many changes; some of the cells were cuboidal and stained well and the lumens were filled with an amorphous pink-staining foamy material. The loops of Henle were composed of large pale-staining foamy cells with basally placed nuclei, and the lumens were obliterated. Staining for fat showed a large number of fat globules within the foamy tubular cells of both convoluted and collecting tubules. Staining for glycogen showed small amounts of glycogen within the cells of the loops of Henle and also extremely sparse accumulations within some of the cells of the convoluted tubules. The interstitial capillaries were engorged, and the interstitial connective tissue was edematous.

Gastrointestinal Tract: Sections from various levels showed changes ranging from complete necrosis and sloughing of the mucosa with intense vascular engorgement of the wall and areas of hemorrhage within the submucosa to extensive inflammatory infiltration of the wall and involvement of the serosa with a fibrinopurulent exudate. In many areas within the ileum, the extensive vascular engorgement of the vessels of the submucosa and the large areas of hemorrhage within the wall were most prominent. These changes appeared to balloon up the wall; here the necrotic changes within the mucosa were most pronounced.

Final Diagnoses: The final diagnoses were diabetes mellitus and acidosis; acute pancreatitis; B. welchii peritonitis; enteritis and early gangrene of the bowel; fecal impaction of the colon and ileum; cardiac dilatation; bilateral emphysema of the lungs; focal acute necrosis of the lungs; gastric contents in



Section through the head of the pancreas, showing extensive replacement of acinar and islet tissue by wide area of necrosis harboring inflammatory cells (*A*). Note the necrotic process and cellular infiltration involving the large pancreatic duct (*B*). Hematoxylin and eosin stain; × 60.

the trachea and bronchi; fibrous pleural adhesions; fatty changes in the liver and kidneys; deposits of glycogen in the liver, spleen and kidneys; atheromatous streaking of the abdominal aorta, and emaciation.

Since acute pancreatitis was classified by Fitz [2] in 1889, there have been many reports dealing with the incidence of this condition in large series of medical, surgical and diabetic patients. Rienhoff and Lewis [3]

2. Fitz, R. H.. Acute Pancreatitis, M. Rec. **35**:197, 1889.

3. Rienhoff, W. F., Jr., and Lewis, D.: Surgical Affection of Pancreas Met with in Johns Hopkins Hospital from 1889 to 1932, Bull. Johns Hopkins Hosp. **54**:386. 1934.

studied the incidence of pancreatic disease at the Johns Hopkins Hospital and found 167 cases in a surgical service of 78,000 patients; there were only 18 patients with acute pancreatitis in this series. Hamperl [4] reported 67 recorded instances of acute pancreatitis or acute necrosis of the pancreas among the records of 20,000 autopsies, representing an incidence of about 1 in 300. At the Deaconess Hospital, Root [1] found 4 reports of acute pancreatitis among the records of 200 autopsies on diabetic patients. As far as the clinical diagnosis is concerned, acute pancreatitis has been rare in diabetes as such. For 2,052 diabetic patients operated on at the Deaconess Hospital, of whom 213 have had abdominal operations, primary acute pancreatitis has never been diagnosed preoperatively and has been found only rarely as a complication of acute disease of the gallbladder.[1]

The relationship of acute pancreatitis to the development of diabetes mellitus has occupied the attention of many investigators, particularly regarding the extent of the damage to the pancreas as a factor in the onset of diabetes and the changes in carbohydrate metabolism during the acute illness. It must be remembered that the incidence of diabetes after acute pancreatitis would be greater were it not for the fact that the lesions which destroy enough of the pancreas to produce insulin deficiency are generally sufficiently severe to cause death from the pancreatitis itself before there has been an opportunity for the diabetes to manifest itself.[5] Bernhard [6] studied 50 cases of operative recovery from acute pancreatitis and found that of the 5 patients who acquired diabetes, 3 died of the disease and 2 were living with a severe form of the disease. The time interval between the pancreatitis and the diabetes ranged from immediate onset to thirteen years. Shumacker [7] collected records of 2,855 cases of acute pancreatitis and found that diabetes mellitus occurred in 62 instances. Of 25 patients who acquired diabetes during the course of acute pancreatitis, 6 died quickly of diabetic coma, 13 died during the acute illness with severe diabetes and 6 patients survived; 2 of the 6 died later in coma. There were 4 patients with onset of diabetes shortly after recovery from acute pancreatitis; in 1 the disease

4. Hamperl, H., cited by Böse, H.: Die Pankreatitis, Zentralbl f. Chir. **63**:261, 1936.

5. Warren, S.: The Pathology of Diabetes Mellitus, ed. 2, Philadelphia, Lea & Febiger, 1938.

6. Bernhard, F.: Die Beziehungen zwischen der Erkrankungen der Gallenwege und dem Auftreten der akuten Pankreasnekrose und Beobachtungen über die diagnostischen Hilfsmittel zur Erkennung der akuten Pankreasveränderungen, Deutsche Ztschr. f. Chir. **231**:1, 1931.

7. Shumacker, H. B.: Acute Pancreatitis and Diabetes, Ann. Surg. **112**:177, 1940.

was mild, in 2 it was well controlled and in 1 it was severe. Thirty-three patients acquired diabetes one to twenty-two years after the initial illness, an average of about seven years. Follow-up studies on 116 patients cured of acute pancreatitis showed a high incidence of disturbance of the carbohydrate metabolism. Diabetes developed in about 9 per cent of the patients, while about 35 per cent of those studied had some alteration of the dextrose metabolism.

The fact that not all of the patients who recover from acute pancreatitis acquire diabetes or even alterations in the tolerance for dextrose brings up the question of the extent of the damage necessary for the production of pancreatic or islet insufficiency. Allen and others [8] have stated that relatively mild changes in the pancreas, some mild enough not to be recognized, may either initiate diabetes or bring about diabetes from "functional wear and tear" months or years afterward. On the other hand, most investigators who have studied the altered carbohydrate metabolism and the onset of diabetes during and following proved acute pancreatitis have been impressed with the severity of the pancreatic necrosis. Sebening [9] emphasized the importance of the loss of pancreatic tissue during the acute illness in the production of diabetes. Bernhard [10] also expressed the belief that the severity of the necrosis, the extent of the sequestration and the persistence of pancreatic fistulas are important factors. It seems, then, that when, as in the case reported here, both islet and acinar tissues have been involved in an acute necrotic process diabetes following proved acute pancreatitis has developed in patients with widespread damage to the pancreas.

There does not seem to be any general agreement as to the cause of acute pancreatitis. Dragstedt, Haymond and Ellis [11] were impressed with the edema and hemorrhage of the pancreas and expressed the belief that the presence of bile and infection with B. welchii are the determining factors in bringing about the necrotic process. Occlusion of the pancreatic duct, due either to gallstones in the papilla of Vater or to metaplasia of the epithelium of the branches of the pancreatic duct, has been

8. Allen, F. M., in discussion on papers of Drs. Warfield and Lemann, J. A. M. A. **89**:661 (Aug. 27) 1927. Mosenthal, H. O.: Pancreatitis and Diabetes, Ann. Int. Med. **11**:1001, 1937. Stern, M.: Fall von Diabetes Gravis mit Pankreatitisschüben, Schweiz. med. Wchnschr. **60**:63, 1930. Sobel, S. P.: Two Cases of Acute Pancreatitis, M. Rec. **147**:11, 1938.

9. Sebening, W.: Folgezustände nach akuter Pancreanekrose, Med. Klin. **23**:551, 1927.

10. Bernhard, F.: Das Auftreten des Diabetes mellitus nach akuten Pankreaserkrankungen, Klin. Wchnschr. **10**:632, 1931.

11. Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Pathogenesis of Acute Pancreatitis, Arch. Surg. **28**:232 (Feb.) 1934.

suggested by Rich and Duff,[12] who expressed the belief that because of the obstruction trypsin and steapsin are liberated, to produce necrosis of the arteries with hemorrhage. Spasm of the sphincter of Oddi has been suggested by Archibald [13] as a means of causing bile to enter the pancreatic duct. Flexner [14] has been able to produce the worst sort of hemorrhagic pancreatitis by injection into the pancreatic duct of bile infected with Bacillus coli. However, from the work of Mann and Giordano [15] it seems likely that the entrance of bile into the pancreatic duct by obstruction of the orifices is seldom the actual cause of acute pancreatitis. It seems more likely that, depending on the nature of the particular lesion, several factors may be concerned in the production of necrosis and/or hemorrhage within the pancreas. The presence of severe enteritis and duodenitis coupled with the changes within the pancreatic ducts may well have been the cause of either bile or infected duodenal contents entering the pancreas and thereby activating trypsinogen to bring about such extensive necrosis and damage to the insular mechanism of the pancreas.

Abdominal pain and vomiting were striking complaints in our patient before the onset of coma. Moreover, symptoms referable to the abdomen are fairly common in the diabetic patient with impending coma; hence the "abdominal syndrome" has been recognized as a frequent occurrence in such patients.[16] In Baker's [17] series, definite abdominal pain was recorded in 34 of 108 cases, or in 41 per cent of the 82 cases in which the presence or absence of this symptom was recorded. Beardwood [18] recorded 71 per cent of 114 patients with diabetic coma who had abdominal complaints; there were 14 patients with acute abdominal conditions. He said: "Acidosis should always be first thought of in a diabetic patient having nausea, vomiting and abdominal pain, and because of the increasing incidence of diabetes this diagnosis should be suspected in every case presenting the symptom of an acute condition of the abdomen." However, abdominal symptoms may be confusing, especially

12. Rich, A. R., and Duff, G. L.: Experimental and Pathological Studies in Pathogenesis of Acute Hemorrhagic Pancreatitis, Bull. Johns Hopkins Hosp. **58**:212, 1936.

13. Archibald, E. W.: Consideration of Pancreatitis, Internat. Clin. **2**:1, 1918.

14. Flexner, cited by Archibald.[13]

15. Mann, F. C., and Giordano, A. S.: Bile Factor in Pancreatitis, Arch. Surg. **6**:1 (Jan., pt. 1) 1923.

16. Walker, H.: Etiology of Abdominal Pain in Diabetic Acidosis, Ann. Int. Med. **9**:1178, 1936.

17. Baker, T. W: Clinical Survey of One Hundred and Eight Consecutive Cases of Diabetic Coma, Arch. Int. Med. **58**:373 (Sept.) 1936.

18. Beardwood, J. T., Jr.: The Abdominal Symptomatology of Diabetic Acidosis, J. A. M. A. **105**:1168 (Oct. 12) 1935.

when the patient is already in coma and there is little history of the preceding clinical picture.[19] That even the presence of acute pancreatitis and peritonitis in our patient was not recognized clinically emphasizes the difficulty in differential diagnosis of abdominal lesions in the presence of diabetic coma. Several aids in the diagnosis of acute pancreatitis in this group of patients have been suggested.[1] These are: prostration more severe than one would expect with a blood pressure over 100 systolic; failure to improve under adequate treatment; sweating, rather than the dry skin so typical of uncomplicated conditions; sudden onset of extreme pain in the upper part of the abdomen and rapid development of coma within six to ten hours, and, lastly, tenderness and spasm limited to the epigastrium and extending to the left of the midline, which may be shown by examination of the abdomen in an early stage, before unconsciousness has set in. In children, other abdominal conditions must be ruled out,[20] and the examiner is faced with the general difficulty of making a differential diagnosis of the acute condition within the abdomen under many handicaps.

Peritonitis has been infrequently encountered as a complication of diabetes mellitus. The cause of the B. welchii infection in our patient may be referred to the extensive inflammatory and necrotic changes within the intestinal tract, particularly the lesions within the ileum. From a study of the pathologic material, the changes within the peritoneum were more recent than those within the pancreas, which were secondary to the involvement of the intestinal tract. The characteristic formation of gas revealed at necropsy, the formation of blebs and the positive Welch-Nuttall reaction of the culture material differentiated this infection from those due to B. coli, which may in some conditions produce gas, especially in the presence of large amounts of glycogen. It is not surprising that the presence of acute pancreatitis and peritonitis was masked in a patient who was in coma at the time of the examination, who presented a meager clinical history and in whom the abdominal symptoms were not at all characteristic.

SUMMARY AND CONCLUSIONS

Diabetic coma, acute pancreatitis and B. welchii peritonitis in a 13 year old white boy are reported. Widespread necrosis of the pancreas with involvement of the islet tissue was responsible for the development of fatal diabetic coma.

19. McKittrick, L. S.: Abdominal Symptoms With or Without Abdominal Lesions in Diabetic Acidosis, New England J. Med. **209**:1033, 1933.

20. Newcomb, A.: Acute Abdominal Pain in Juvenile Diabetes Mellitus, Illinois M. J. **68**:544, 1935.

Postmortem examinations have been performed on 10 children who died during diabetic coma; acute pancreatitis and peritonitis were found in only 1 child, which represents an incidence of 10 per cent in this series.

The presence of severe enteritis and duodenitis coupled with the changes within the pancreatic ducts was probably the cause of the entrance of bile or infected intestinal contents into the pancreas; thereby trypsinogen was activated and extensive necrosis of the pancreas developed.

The differential diagnosis of abdominal lesions in the presence of diabetic coma is severely handicapped by the occurrence of the "abdominal syndrome" in uncomplicated diabetes and by the general problem of acute conditions within the abdomen in children.

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STUDIES ON OXYURIASIS

XXVIII. SUMMARY AND CONCLUSIONS

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BETHESDA, MD.

The project which has led to publication of the series of papers under the general title "Studies on Oxyuriasis" was initiated in 1936 by the late Dr. Maurice C. Hall, then chief of the Division of Zoology, as a result of his conviction that there was a need for a well rounded investigation in this field and his belief that group research would contribute effectively to this need. The resulting reports, a list of which is appended,[1] have appeared in a wide variety of publications, not

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From the Division of Zoology, National Institute of Health, United States Public Health Service.

1. (*a*) Hall, M. C.: I. Studies on Oxyuriasis: Types of Anal Swabs and Scrapers, with a Description of an Improved Type of Swab, Am. J. Trop. Med. **17**:445-453 (May) 1937. (*b*) Wright, W. H.; Bozicevich, J., and Rose, J.: II. A Preliminary Note on Treatment with Tetrachlorethylene, Virginia M. Monthly **64**:339-341 (Sept.) 1937. (*c*) Bozicevich, J.: III. The Incidence of Pinworm Infestation in a Group of Two Hundred and Thirty Boys in Washington, D. C., M. Ann. District of Columbia **6**:239-241 (Aug.) 1937. (*d*) Wright, W. H., and Cram, E. B.: IV. Some Aspects of the Problem of Therapy, Am. J. Dis. Child. **54**:1276-1284 (Dec.) 1937. (*e*) Wright, W. H.; Bozicevich, J., and Gordon, L. S.: V. Therapy with Single Doses of Tetrachlorethylene, J. A. M. A. **109**: 570-573 (Aug. 21) 1937. (*f*) Cram, E. B.; Jones, M. F.; Reardon, L., and Nolan, M. O.: VI. The Incidence of Oxyuriasis in 1,272 Persons in Washington, D. C., with Notes on Diagnosis, Pub. Health Rep. **52**:1480-1504 (Oct. 22) 1937. (*g*) Wright, W. H.; Bozicevich, J., and Gordon, L. S.: VII. Clinical Improvement Following Treatment with Single Doses of Tetrachlorethylene, Am. J. Trop. Med. **18**:609-617 (Sept.) 1938. (*h*) Wright, W. H.; Brady, F. J., and Bozicevich, J.: VIII. A Preliminary Note on Therapy with Gentian Violet, Proc. Helminthol. Soc. Washington **5**:5-7 (Jan.) 1938. (*i*) Cram, E. B.: IX. The Familial Nature of Pinworm Infestation, M. Ann. District of Columbia **10**:39-48 (Feb.) 1941. (*j*) Reardon, L.: X. Artifacts in "Cellophane" Simulating Pinworm Ova, Am. J. Trop. Med. **18**:427-431 (July) 1938. (*k*) Wright, W. H., and Bozicevich, J.: XI. Dermal and Intradermal Skin Reactions in Oxyuriasis, J. Parasitol. **23**:562 (Dec.) 1937. (*l*) Cram, E. B., and Reardon L.: XII. Epidemiological Findings in Washington, D. C., Am. J. Hyg. **29**:17-24 (Jan.) 1939. (*m*) Jones, M. F.; Cram, E. B., and Wright, W. H.: XIII. Problems Presented by a Family of Seven, All Infested with Pinworms, J. Parasitol. **23**:571 (Dec.) 1937. (*n*) Wright, W. H.; Brady, F. J., and Bozicevich, J.: XIV. Controlled Tests with Various Methods of Therapy, Pub. Health Rep. **54**:2005-2016 (Nov. 10) 1939. (*o*) Bozicevich, J., and Brady, F. J.: XV. A Study of Five Hundred and Four Boys in a Boy's

(Footnote continued on next page)

all of which are readily available to the physician, particularly to the pediatrician, who is most interested in the subject. For this reason it is proposed in this final publication to summarize the salient facts reported in previous papers in the series so that the findings of most importance may be brought together in a single communication.

Since the work was inaugurated, many other investigators have contributed to the subject and have confirmed, complemented and in some cases extended the results of research brought out in this project. It is not within the scope of this paper to review the results of these other workers. However, in no case have their conclusions been at variance with the facts summarized here.

BIOLOGY

Because of certain unique biologic adaptations, Enterobius vermicularis, the pinworm parasite of man, presents a special case as regards diagnosis, epidemiology and control. The exact life history of the parasite has never been elucidated because of the lack of susceptible experimental animals. However, there have been reviewed (XVII) [1q] studies conducted in Europe in the latter half of the last century, which

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indicated that female worms migrate from the anus fifteen to twenty-eight days after the ingestion of infective pinworm eggs by mouth. The peculiar adaptation which enables the female worm to migrate out of the intestinal canal and to deposit its eggs on the skin of the host has assured survival of the parasite despite the elaborate sanitary facilities developed by modern man.

Attempts to Infect Abnormal Hosts.—In an effort to provide material for biologic studies and to secure experimental animals for use in anthelmintic tests, experiments on infection were undertaken with various laboratory animals. Although pinworm larvae survived for a few days in the intestinal tract of guinea pigs and mice, it was not possible to establish infections in these animals or in dogs or in rhesus monkeys. With the view of determining whether a dietary deficiency would influence the development of the worms in an abnormal host, experiments were undertaken to infect albino rats maintained on a diet deficient in vitamin A (XXVI).[18] However, the lack of vitamin A did not increase the susceptibility of the test rats to infection with E. vermicularis.

Migration.—Observations as to the time and method of migration and of ovipositing by female pinworms were made on infected boys in a summer camp (XV)[10] and furnished the following particulars: As early as 8 p. m. gravid female worms were located about an inch (2.5 cm.) above the mucocutaneous junction, and at 9 o'clock they were at the junction. The boys retired at this hour, and about a half-hour later worms were found on the skin, usually in moist areas, as far forward as the scrotum and posteriorly and laterally as far as 2½ inches (6.3 cm.) from the anus. Locomotion was apparently accomplished by successive anchorings of head and tail; a worm seemed to affix the head to the skin or mucosa and move the tail vigorously, apparently feeling for an adjacent surface. The degree of activity varied with the location of the worms; those higher up in the canal were extremely active while those that had migrated out soon became inactive. Within a few minutes after exposure to the air, increased opacity and diminished somatic activity of the worms were noted. Violent uterine contractions resulted in the extrusion of white masses of eggs. These eggs were expelled in a cylindric stream and frequently hung in festoons. Shriveled bodies of pinworms were sometimes found in the pajamas of the boys after an intensive search in the morning.

Egg Production.—Actual counts were made of the number of eggs in 20 gravid specimens of E. vermicularis (XVI).[19] The number was strikingly variable, ranging from a low count of 4,672 to a high count of 16,888; the arithmetical mean was 11,105 and the mean of the extremes 10,780. The variation in the counts may have been due at

least partly to differences in the source of the worms and the manner of handling them, and the low counts may therefore not be representative of the total number of eggs produced by the worm. However, from a practical point of view, the arithmetical mean of approximately 11,000 eggs per worm offers convincing evidence of the degree to which an infected person may serve as a source of reinfection to himself and of infection to others.

Dissemination of Eggs in the Household.—Examination of dust collected in seven households containing pinworm-infected members demonstrated strikingly the wide distribution of pinworm eggs and provided evidence that infection by inhalation is theoretically possible (XX).[1t] Of 241 samples of dust collected with small camel's hair brushes, pinworm eggs were found in 221, or 91.7 per cent. All rooms, including the kitchen and bathroom, yielded samples which contained eggs; eggs were found at all levels from that of the floor to that of ceiling lights. The largest number of eggs was found in bedrooms. More than three fourths of the eggs contained fully developed embryos; from the appearance and from artificial hatching of eggs selected at random, it was concluded that about one half of the eggs were viable or had recently been so.

Physical and Chemical Factors.—The membranes of the pinworm egg were found to be composed of three layers, which were studied chemically with the following results (XXI):[1u] The outermost layer was found to be a protein, the identity of which is still in question. The shell proper is composed of chitin, apparently laid down in two layers. The innermost membrane is lipoid, and tests indicated that it is a sterol.

At the time of oviposition, the pinworm egg contains a partially developed "tadpole stage" larva, which is not infective until it undergoes some further development. At body temperature this development is rapid, and within six hours the infective "ring and a half stage" larva is formed; at temperatures around 20 C. (68 F.) the development is slower, requiring up to thirty hours. Since the infective stage is the one of importance from the standpoint of the transmission of the parasite, biologic studies were conducted on eggs in this stage.

Resistance of the eggs to physical agents was experimentally tested (XXIII),[1w] first within the range of temperature and humidity ordinarily found in environmental conditions and secondly at temperatures which would indicate unusual weather conditions or artificial heat. Survival under the experimental conditions was measured by subsequent ability of the eggs to hatch active larvae in artificial digestive juice. Results indicated a detrimental effect on pinworm eggs from lowering the humidity and/or raising the temperature.

Cool, dry conditions (temperature 20 to 24.5 C. and relative humidity 30 to 54 per cent) were relatively unfavorable for survival; less than 10 per cent of the eggs survived forty to forty-eight hours, and few or none survived ninety hours.

Cool, moist conditions (temperature 20 C. and relative humidity 47 to 67 per cent), on the other hand, proved favorable for survival, there being little decrease even at forty-eight hours. If after twenty-four hours the humidity was increased to a range of 62 to 91 per cent, even after six days' exposure 31 per cent of the eggs were capable of hatching.

An increase in temperature (26 to 29 C.) with the relative humidity remaining at about the same high level, resulting in warm, moist conditions, was attended by a drop in survival of eggs after thirty to forty hours. Increasing the temperature slightly (28 to 31 C.) and lowering the humidity (50 to 72 per cent) gave appreciable lethal effects after seventeen to twenty hours, and, although a few eggs survived two and three days, none survived four days. These results were comparable, therefore, to those obtained under cool, dry conditions.

A more rapid decrease in survival occurred under warm, dry conditions (temperature 27 to 29 C. and relative humidity 38 to 50 per cent); results of various experiments showed that at the end of twelve hours 11 per cent or less of the eggs survived and by forty hours no eggs survived. With further raising of the temperature and lowering of the humidity an even more rapid decrease in survival was observed, until at 44 to 48 C. and 22 to 23.5 per cent relative humidity for two hours only a few eggs survived, and at three hours none survived. No eggs survived after one minute under hot, dry conditions, with the temperature at 65 C. and the relative humidity at 20 per cent.

A limited number of tests with freezing temperatures indicated that pinworm eggs can withstand freezing for only one or two days. At temperatures of -8 to -10 C. ($+17.6$ to $+14$ F.), 66 per cent survived after eighteen hours' exposure; 50 to 70 per cent survived after forty-five hours; many survived after seventy hours but appeared to have low vitality, and none survived after one hundred and forty-two hours, or approximately six days. Eggs floating on water survived longer at 3 to 5 C. than did those kept at higher temperatures. Individual variation in the resistance of eggs was evidenced by the fact that it was relatively difficult to obtain a 100 per cent kill even after 90 to 95 per cent of the eggs were apparently dead.

The studies emphasize great variation in survival under varying conditions, especially as regards temperature and humidity. It is evident, however, that eggs on water survived longer than dry eggs at the same temperature; that at any temperature survival is greatest under the most humid conditions, and that at any humidity survival is greatest

at the lower temperatures. These facts may be of practical significance as regards the influence of geographic and seasonal weather conditions on the spread of infection and may be of value in the formulation of control measures.

As regards destruction of pinworm eggs by chemicals, tests were made of the effect of certain gases in common use in fumigation procedures (XXVII).[1a'] Embryonated pinworm eggs were subjected to hydrocyanic acid gas under conditions of commercial fumigation at a local storage warehouse. Eggs were exposed in glass dishes placed approximately 20 feet (6 meters) from the center of gas generation, and eggs on a dry base were compared with those floated on water. Survival was determined subsequently by the ability of the eggs to hatch active larvae in artificial digestive juice. The fumigation failed to kill the embryos in the eggs, since there was no significant difference in percentage of survival of eggs exposed to hydrocyanic acid gas and control lots not exposed to the gas. In controlled laboratory tests, paradichlorobenzene and naphthalene were equally ineffective.

DIAGNOSIS

The inadequacy of fecal examination for the diagnosis of oxyuriasis was evident. In one series of examinations (IV) [1d] about 1 person of 7 and in another series (VI)[1f] only about 1 person of 10 had eggs in the feces, whereas from all of them pinworm eggs were detected by microscopic examination of scrapings from the perianal region; and of the subjects examined in the former series subsequent treatment demonstrated that most had been heavily infected.

The technic of diagnosis was standardized (I) [1a] by the use of a new type of swab, designated the NIH (National Institute of Health) swab. This swab consists of a glass rod with its rounded tip covered with a 25 mm. square of plain transparent nonwaterproof cellophane, the rod being inserted in a perforated cork fitted in a small test tube. The cellophane tip is stroked firmly over the perianal surface. In the laboratory the cellophane is detached from the rod, mounted in water or tenth-normal sodium hydroxide solution and examined under the microscope for the presence of pinworm eggs. This swab meets all the specifications required in a satisfactory diagnostic procedure in that it picks up pinworm eggs dependably, delivers them to the microscope slide with a minimum amount of manipulation, is easy to transport with no loss of eggs and with safety to persons handling the swab, and causes the patient little or no inconvenience.

The difficulty of detecting all cases of pinworm infection, even with this improved method of diagnosis, has been stressed (VI [1f] and

XVII [1q]). Partly responsible is the periodicity of infection, due to the fact that the presence of pinworm eggs marks the end of the period of infection as far as that particular worm is concerned and to the fact that continuation of infection depends on reinfection and successive migration of female worms as they reach maturity. There is therefore an inconstant level of infection, and repeated swab examinations are often necessary to detect an infection. Other factors influencing the efficiency of the swab technic include the time of day at which the swab is taken and the proficiency of the person making the swab. In one series (VI) [1f] the first swab detected 50 per cent of the infected persons; in another series (XV) [1o] 68 per cent were detected by four swabs made on different days but not all on successive days. In determining the familial extent of infection (IX,[1l] XIII,[1m] XVII [1q]) there was considerable difference in the facility with which diagnosis was arrived at in different members of the family, since seven swabs were necessary to detect infection in some members.

It was found that the most suitable time for making the swab is immediately after the patient arises and before he bathes or goes to the toilet. The most effective technic was found to consist in a firm stroking motion directed outward from the anal opening, parallel to and penetrating the folds, and repeated so that most of the area immediately surrounding the opening is swabbed. That deposition of ova is not strictly localized was evident from observations that worms may migrate as far forward as the scrotum on males (XV) [1o] and the vagina on females and that vulval swabs may contain eggs (XVII) [1q] even when anal swabs contain none.

Artefacts simulating pinworm eggs were occasionally found (X) [1j] in the cellophane used for swabs, their presence constituting a possible source of error in diagnosis. Usually ovoid and enveloping a dark amorphous mass with hyaline outline, they were similar in appearance to the pinworm egg. However, they were infrequent in occurrence and were entirely lacking in most rolls of cellophane. Apparently they represented small blemishes in the material.

Diagnosis of oxyuriasis by dermal and intradermal reactions was investigated (XI).[1k] An antigen prepared from adult and larval forms of E. vermicularis was used for dermal tests in a 1:100 dilution and for intradermal tests in dilutions ranging from 1:500 to 1:10,000. Of 140 persons tested, 90 were known to be infected with pinworms while 50 were free of this infection; of the 50 controls, 21 had no worm parasites and 29 were infected with worms other than pinworms. The results indicated high specificity of the dermal test. With dilutions of antigen up to and including 1:5,000, the intradermal test was not specific, since positive reactions were obtained on some persons infected with one or more species of worms other than pinworms.

Information bearing on the diagnosis of oxyuriasis at necropsy was obtained (XXV) [1y] from examination of intestines of 72 children; pinworms were found in 21 subjects, or 29 per cent. Worms were recovered more frequently from the large intestine than from the small; examination of the entire large intestine gave more positive results than would have been obtained from examination of any one part, although the appendix proved a fairly reliable index of infection.

EPIDEMIOLOGY

The epidemiology of oxyuriasis was investigated by comprehensive sampling of the population of Washington, D. C., the studies taking into consideration the factors of race, sex, age and various environmental conditions. Persons examined were for the most part from two sources: (*a*) an outpatient clinic held at Providence Hospital, where swabs were provided for home use not only for the person suspected of having pinworms but also for other members of the family, and (*b*) special groups of children in camps and in nursery schools, the swabs in these cases being made by trained personnel. The sampling was not of a random nature, but it was considered as representing a fair cross section of the population.

Examinations with NIH swabs were made on approximately 4,000 persons, with the following results: Of 2,895 white persons, 1,202, or 41.5 per cent, were infected with pinworms, and of 1,099 Negroes, 142, or 12.9 per cent, were infected. When other factors were comparable, there appeared to be no appreciable difference in infection in the two sexes. A correlation with age was indicated to the extent that the incidence was highest in children of school age, lowest in adults and intermediate in children of preschool age (XII).[11] Children under 14 years of age appeared more susceptible; after that age the incidence began to diminish (XV).[10] That the school may be a factor of significance in the prevalence of oxyuriasis was indicated by the fact that in three nursery schools, two of which were public and one private, white children who were of an age usually classified as preschool age showed an incidence of pinworms equal to that of children of school age; slightly more than 50 per cent of the children were infected (XXIV).[1x] The highest incidence was shown by a group of 504 boys 6 to 16 years old, 57 per cent of whom were found infected with pinworms when two to four swab examinations per person were made during the first week after their arrival in a summer camp (XV).[10] The previous year a single swab examination of 230 boys in this camp had shown 72, or 31.3 per cent, infected with pinworms (III).[1c]

The difference in incidence of pinworms in the two races grew more pronounced with increase in the size of the sample (VI,[1f] XXIV,[1x]

IX [11]). As indicated in the following tabulation, the incidence in white persons remained practically constant while in Negroes the incidence fell as the sample grew.

White		*Negro*	
Number Examined	Per Cent Infected	Number Examined	Per Cent Infected
476	41.2	90	21.1
2,582	41.9	789	15.5
2,895	41.5	1,099	12.9

As regards the familial extent and distribution (IX),[11] information was available from three hundred and twenty families, including two hundred and eighty-six white and thirty-four Negro families, in which examinations were made of additional members of the family after pinworms were found in 1 member. The results were based on a total of 5,539 swabs, an average of 3.7 swabs per white person and 3.5 swabs per Negro, a number insufficient to detect all cases of infection. In spite of this limitation there was quantitative evidence that pinworm infection is frequently familial; the evidence was especially conclusive as regards the white race. In the two hundred and eighty-six white families, 1,353 persons were examined; of 860 children, 618, or 72 per cent, had pinworms, and of 493 adults, 179, or 36 per cent, were infected. Thus the incidence in children was twice as great as in adults. In the thirty-four Negro families, 172 persons were examined; of 114 children, 58, or 51 per cent, were infected, while of 58 adults, only 4, or 7 per cent, were infected. In the white families multiple cases of infection were found in three times as many families as was a single case; on the other hand, in the Negro families the number with a single case was slightly greater than the number with multiple cases. The two hundred and fifteen white families with multiple cases averaged 3.4 infected persons per family; in sixty-three of the sixty-seven families with a single case it was a child who was found infected and in four it was an adult. There was a substantial number of white families, in fact almost one half of the families in which examinations were made, in which all children who were examined were infected, and in the remaining families evidence of infection was found in more than one half of the children examined. One or both parents were found infected in approximately one half of the families in which adults were examined. It is therefore evident that if there is one person in the family infected with pinworms, there are probably other infected members; that most or all of the children may be infected, and that there is a substantial likelihood that one or both parents are infected.

The majority of the pinworm-infected families resided in older, comparatively congested residential sections of the city (XII).[11] However,

the cases were by no means confined to those sections, nor were they limited to any one social-economic level. Evidence was found (XV)[10] of a correlation with the size of the family: the more members, the more chance of introducing the infection and the more favorable the conditions for its spread within the household. Crowding increased the incidence of infection in a geometric rather than in an arithmetical progression.

CLINICAL CONSIDERATIONS

From physical examinations and case histories of 200 pinworm-infected persons (XVIII)[1r] and from observed clinical improvement following treatment of about 50 persons (VII),[1g] certain conclusions were drawn as to the symptomatology of oxyuriasis. A slight eosinophilia apparently resulted from the infection. No anemia was attributable to it; however, in spite of normal hemoglobin content, dark circles under the eyes and pallor of the face were frequently seen, and there was remarkable improvement in these respects following treatment. Underweight children often gained after treatment; 27 of 49 pinworm-infected boys were underweight at time of treatment, and subsequent examination of those boys who were available showed that 37 of 44, or 84.1 per cent, had gained an average of 2.7 pounds in two weeks following treatment.

There was conclusive evidence, confirming that of previously published reports, that oxyuriasis may be the cause of gastrointestinal symptoms in some persons. However, there was no evidence of relationship between appendicitis and oxyuriasis or between abdominal pain and oxyuriasis. In many cases the appetite was much improved after treatment for pinworms. Craving for sweets was as frequent in control subjects as in persons with oxyuriasis. Local symptoms during migration varied from a mild tickling to acute pain; there was occasional extreme itching of the skin in the perianal region and other parts of the body, which was believed to be allergic.

Enuresis was not found with any greater frequency in infected persons than in noninfected. A mucoid vaginal discharge, often present in infected girls, was attributed to irritation resulting from entrance of pinworms into the vulva; from 14 of 45 pinworm-infected girls, a single vulval swab made at the introitus contained pinworm eggs. It was concluded that there are probably many cases of pinworm vaginitis not diagnosed as such.

Biting of nails, sucking of a thumb, picking at the nose and grating of teeth were not found more frequently in infected persons than in control groups. Restlessness and insomnia were common. Effects on behavior attributable to the parasitic infection included lack of cooperation, inattention and a feeling of shame and inferiority, often occasioned

by ridicule as a result of noticeable scratching by the patient to relieve pruritus. Striking improvement was seen in individual patients after treatment for removal of the worms. In one group it was found by inquiry from school teachers that 10 of 24 boys exhibited definite improvement in their social attitude and scholastic standing within the two months following treatment.

PREVENTION

The results of the investigation provided evidence to an ever increasing degree that it is an extremely difficult matter to prevent the spread of oxyuriasis. Because of the large number of eggs scattered by an infected person (XVI)[1p] and the wide dispersal of the eggs throughout the household (XX)[1t] and because of the resistance of the eggs to physical (XXIII)[1w] and chemical (XXVII)[1a'] agents, even stringent sanitary measures cannot be relied on to control the infection. If it is possible from the study of the chemistry of the membranes of the pinworm egg (XXI)[1u] to find a chemical or combination of chemicals which will penetrate the proteinaceous layer, the chitin shell and finally the lipoidal membrane, an effective ovicide may become available. Until that time hygienic measures must be considered only as an adjunct to medicinal treatment. This was pointed out early in the investigation (IV),[1d] and all later evidence supported the conviction. The joint use of therapeutic and prophylactic measures during an eighteen month period in a nursery school (XIX)[1s] apparently reduced the incidence of oxyuriasis, although it did not eradicate the infection. Judging from frequent swab examinations during the last five months, there were no new cases and the figures for incidence were substantially lower than during any similar period previously studied. The control program included use of nonmedicated enemas for most subjects, but for 4 persons with persistent infections gentian violet was employed; sanitation was strictly enforced, including use of saponated solution of cresol for cleaning, thorough sunning of cots and blankets, use of individual towels and frequent and thorough washing of the hands of the children.

THERAPY

It was pointed out (IV)[1d] that the criteria usually accepted as indicating eradication of pinworms consist in a temporary clinical improvement, failure to observe worms in the stools or failure to find pinworm ova on microscopic examination of the stools. That the last criterion is unreliable has already been discussed. The procedure adopted in the present investigations included checking the results of treatment by the use of seven consecutive daily NIH swabs, beginning from the tenth to the forty-second day after the end of treatment. It was emphasized that

100 per cent efficiency is needed in the treatment of oxyuriasis, a requirement not present in respect to treatment of other common helminthiases; with oxyuriasis anything less than complete eradication affords only transitory relief, since the residual infection will build up again. For this reason adequate diagnostic tests should be conducted on all members of the household, and all infected members should be treated simultaneously. The importance of observing these two requirements was early demonstrated (XIII)[1m] in a family of 7 members, all infected with pinworms, to whom various treatments were given and on whom approximately 800 swab examinations were made. Five persons were apparently freed of pinworms for varying lengths of time; the remaining 2 were never free from worms for more than ten or fifteen days or for more than five successive examinations. There was no time at which every member examined was free from the parasites; therefore, there apparently was a constant source of reinfection.

Confirmatory evidence from the treatment of several hundred persons with oxyuriasis led to the following specifications for a satisfactory treatment (VIII):[1h]

1. The drug must be highly effective in removing pinworms.

2. The drug must be relatively nontoxic, so that it can be given in repeated treatments over a period during which viable pinworm ova may be present in the patient's surroundings, the repeated administration of the drug also assuring its entrance into the cecum and appendix, common sites of pinworm infection.

3. The treatment must be of such reasonable cost that its use in large families will not be prohibitive.

4. The treatment must be so easily administered that it can be used with a minimum of effort in large household groups.

Various forms of treatment which are frequently used do not meet these specifications and are ineffective. Anal ointments, such as 2 per cent phenol ointment U. S. P., may be indicated for relief of irritation but have no appreciable value in destroying the embryos in the eggs deposited in the perianal region. Mechanical and chemical devices can not be relied on to hinder migration.

Tetrachlorethylene.—As regards single dose treatments by mouth, neither oil of chenopodium nor carbon tetrachloride is satisfactory for the removal of pinworms. Critical tests of tetrachlorethylene (II,[1b] V [1e]) showed it to be the best single dose treatment available. Tests were carried out in the following manner: All patients were hospitalized at 4 p. m. They were given a light supper and later in the evening a high soapsuds enema. The following morning no breakfast was allowed; the drug was given at 8 a. m., and food was withheld until after the bowels

had moved copiously. The tetrachlorethylene was administered in a dosage of 0.1 cc. for each year of apparent (not chronologic) age, the drug being given in 30 cc. of a saturated solution of magnesium sulfate plus 60 cc. of water or, by preference because of reactions from the magnesium sulfate, in a suitable dose of a solution of magnesium citrate. Of the first group of patients, 6 of 11 were free from pinworms after treatment; from three to forty post-treatment swabs were made. Of a supplementary group, 30 of 44 patients, or 68.2 per cent, were free from infection when examined by two post-treatment swabs each; a correction figure of 30 per cent was applied to this figure, giving an efficacy of 47.7 per cent for the drug, since two swabs will detect only about 70 per cent of cases of pinworm infection. The pinworms removed by the treatment were counted in all cases; in the first group there was an average of 352 worms per person, and in the second, larger, group an average of 255 worms per person, the counts in the latter series ranging from 1 to 4,958 worms per person. From a comparison of results in individual cases it was concluded that tetrachlorethylene is more efficient in effecting cures in persons lightly infected than in persons heavily infected; only 2 of the 30 cured subjects showed infections above the mean.

Hexylresorcinol.—Various anthelmintic tests were carried out with hexylresorcinol (XIV).[1n] Eighteen of 27 patients treated with a varying number of enemas consisting of the drug in a dilution of 1:2,000 in water were free from worms on post-treatment swab examinations. Ten enemas spaced over a period of three weeks constituted the minimum number necessary usually to eradicate pinworm infection, although some patients required more prolonged treatment. Hexylresorcinol administered in the form of pills in a single dose orally failed to eradicate pinworm infection in the 4 subjects treated in this manner. Supplementing the oral treatment with an enema once a week for three weeks added little to the efficacy of the drug. Also the use of 1 ounce (30 cc.) of 1:1,000 hexylresorcinol jelly inserted into the rectum at bedtime over varying periods of time was found ineffective.

Santonin.—Twenty patients were treated with santonin in a single dose daily over a period of ten days (XIV).[1n] Nine of them were still infected and 11 were free of worms on post-treatment swab examinations. However the efficacy of the treatment was probably under 50 per cent, since an inadequate number of swabs was obtained on some subjects.

Gentian Violet.—Since none of the conventional methods of therapy measured up to the specifications outlined here, tests were conducted with gentian violet, one of the few known anthelmintics which can be given with safety in repeated doses over a period of time. The results

(VIII,[1h] XXII[1v]) were superior to those obtained with other methods of therapy. The dosage of the drug for adults was two 32 mg. tablets three times a day before meals and for children 10 mg. a day for each year of apparent (not chronologic) age, the total daily amount of the drug for children being divided into three doses. The routine of treatment was varied in different series of tests with the view of determining the most suitable regimen. Part of the patients were given the drug for ten consecutive days, and part were treated for eight days, allowed to rest for seven days and then retreated for an additional period of eight days. Both enteric-coated and water-soluble coated tablets were employed. In all cases, seven consecutive daily post-treatment swabs were taken at varying periods after the end of the treatment. Of the total of 224 persons treated, 189, or 84 per cent, were free from pinworms on the swab examinations.

Approximately 39 per cent of the treated subjects experienced a gastrointestinal upset of varying degree. These reactions were temporary and subsided quickly when dosage of the drug was reduced or the treatment was discontinued for a day or two. Conditions believed to serve as contraindications for the use of gentian violet include concomitant infections with Ascaris lumbricoides, moderate to severe cardiac, hepatic or renal disease, alcohol in the digestive system and diseases of the gastrointestinal tract.

SYNOPSIS

The results of a group research project have been presented in a series of papers under the general title "Studies on Oxyuriasis." Emphasis has been placed on the unique characteristics of infection with E. vermicularis. The method of diagnosis was improved and standardized by the development and subsequent extensive use of a new type of anal swab, designated the NIH (National Institute of Health) swab. Observations were made on the migration of the parasites. The observations relative to the chemical nature of the shell of the pinworm egg, the resistance of the egg to physical and chemical agents, the actual numbers of eggs produced by the worms and the widespread distribution of the eggs in household dust threw light on the epidemiologic aspects and on the difficulty of controlling the infection. The incidence of oxyuriasis was high in approximately 4,000 persons belonging to various population groups in Washington, D. C. The symptomatology was studied on some 250 persons infected with the parasite. That preventive measures alone cannot be relied on to control the infection was stressed. Previously known methods of therapy were tested, and a new and more effective treatment with gentian violet was established.

STREPTOCOCCIC ANTIFIBRINOLYSIN IN NEWBORN INFANTS

TRUE AND FALSE TESTS

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In 1933, Tillett and Garner [1] found that certain strains of beta-hemolytic streptococci produce a substance capable of liquefying human fibrin and demonstrated the presence in human serum of a specific antibody that was termed antifibrinolysin. Antifibrinolysin is measured by the time required for an effective strain of the organisms to produce complete lysis of the subject's plasma clot. The clot of a normal person is completely lysed in from twenty to sixty minutes, while that of a patient convalescing from an infection with beta hemolytic streptococci may resist lysis for twenty-four hours or more. The blood serum of such a patient is considered to have a high content of antifibrinolysin. Intermediate lysing times represent corresponding levels of antibody.

Applying this test to a series of mothers and newborn infants, Lippard and Wheeler (1936) [2] found that the plasma clots of half of the newborn infants showed a definite prolongation of the lysis time, while that of only 1 of the corresponding mothers exhibited this resistance. A plasma clot from each of the remaining mothers was lysed within sixty minutes. Simultaneous application of another test for beta streptococcic antibody (the antistreptolysin test of Todd [3]) to the

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1. Tillett, W. S., and Garner, R. L.: The Fibrinolytic Activity of Hemolytic Streptococci, J. Exper. Med. **58**:485, 1933.

2. Lippard, V. W., and Wheeler, G. W.: Beta Hemolytic Streptococcic Infection in Infancy and Childhood: III. Placental Transmission of Antifibrinolysin and Antistreptolysin, Am. J. Dis. Child. **52**:61 (July) 1936.

3. Todd, E. W.: Antihaemolysin Titres in Hemolytic Streptococcal Infections and Their Significance in Rheumatic Fever, Brit. J. Exper. Path. **13**:248, 1932.

same series of subjects revealed that the antibody levels of mother and newborn child were approximately equal. As measured by either type of test, however, the antibody level of the blood in most of the infants diminished rapidly during the first few weeks of life.

In 1940 Boisvert [4] made a further study of streptococcic antifibrinolysin content of mother and newborn infant, finding for each pair that the lysis time of the mother was normal while that of the child was greatly prolonged. Boisvert noted that the plasma of half of these infants had completely lost the resistance to fibrinolysin by the tenth day after delivery and that the plasma of all of them had lost it by the age of 6 weeks.

As an explanation of the discrepancy in antifibrinolysin content of mother and newborn child, Lippard and Wheeler [2] suggested that the substance in the blood of the infant that inhibits dissolution of the clot is not identical with that produced in response to infection by the beta hemolytic streptococcus. Boisvert raised the question as to whether it represents a true beta streptococcic antibody that has been stored up in the fetus.

In 1941 Milstone [5] showed that a clot prepared from highly purified fibrinogen of a normal person resists streptococcic fibrinolysis indefinitely. If a small amount of normal human serum is added to the test mixture, however, lysis promptly occurs. He concluded that something in normal human serum is essential to effect streptococcic fibrinolysis and showed that this "lytic factor" is present in the euglobulin fraction of the serum. He further demonstrated that it can be inactivated by heating the serum for an hour at 56 C. He suggested that the absence of this factor may account for some of the unusual reactions to the test.

Since it has been shown by Lewis and Wells [6] and by Boyd [7] that the cord blood of a newborn infant contains little or no euglobulin (table 1), it occurred to us that the "lytic factor" of Milstone might not always be present in sufficient amounts to effect streptococcic fibrinolysis. The plasma clot of the newborn would then be comparable to the clot prepared from highly purified fibrinogen, which Milstone found to be lysis resistant. Streptococcic fibrinolysis of the plasma clot of a newborn child would be prevented or delayed, not by the presence

4. Boisvert, P. L.: Streptococcal Antifibrinolysin Test in Clinical Use, J. Clin. Investigation **19**:65, 1940.

5. Milstone, H.: A Factor in Normal Human Blood Which Participates in Streptococcal Fibrinolysis, J. Immunol. **42**:109, 1941.

6. Lewis, J. H., and Wells, H. G.: The Function of the Colostrum, J. A. M. A. **78**:863 (March 25) 1922.

7. Boyd, G. L.: The Value of Colostrum to the Newborn, Canad. M. A. J. **12**:724, 1922.

of a true specific antifibrinolysin, but by the absence of sufficient "lytic factor." This hypothesis would readily explain the discrepancy of finding an apparent elevation of antibody in the blood of an offspring whose mother did not have the same property in her blood. To test this point we have examined the blood of a series of 50 unselected newborn infants and 26 of their mothers, using the standard test and the modifications of it described in the following section.

METHOD

The samples of plasma and serum of the newborn infants were obtained immediately after delivery from umbilical cord blood. Samples of venous blood were obtained from the mothers during the first week post partum.

In the routine tests for streptococcic antifibrinolysin, the adaptation of Tillett and Garner's method was essentially the same as that described in a previous

TABLE 1.—*Protein Content of Human Blood (From Lewis and Wells*[6])

	Euglobulin Nitrogen, Gm.	Total Globulin, Nitrogen, Gm.
Adult		
1	0.254	0.687
2	0.223	0.648
3	0.236	0.551
4	0.247	0.449
5	0.280	0.547
Newborn		
1	0.006	0.207
2	0.000	0.403
3	0.009	0.269
4	0.000	0.429
5	0.000	0.383

report.[8] For interpreting the results, any blood from which the plasma clot resisted lysis for three hours or more was considered to possess a definite increase in antibody. The following modifications of the test were also employed: (*a*) the inclusion of 0.2 cc. of fresh serum from a normal older child or adult in the routine test of a newborn infant's plasma; (*b*) the inclusion of 0.2 cc. of a newborn infant's serum in the routine test of the plasma of a normal older child or adult. In each case the volume of serum was substituted for an equal amount of the 0.85 per cent solution of sodium chloride used in the test, so that the final volume of the test mixture remained unchanged. (*c*) In this modification of the routine test the isotonic solution of sodium chloride was entirely replaced by 0.6 cc. of the sodium diethylbarbiturate buffer described by Milstone and 0.2 cc. of "lytic factor." In preparing the "lytic factor," precipitation of the euglobulin fraction of fresh human serum was effected by the method of Milstone, in which dilute acetic acid is used, and the precipitate was subsequently dissolved in an amount of the buffer solution equal to the original volume of the serum used.

8. Lichty, J. A., Jr.: Relation of Streptococcic Antifibrinolysin to Acute Rheumatic Fever, Am. J. Dis. Child. **62**:92 (July) 1941.

RESULTS

Tests for streptococcic antifibrinolysin were performed on the blood of 50 unselected newborn infants and 26 of their mothers at the Strong Memorial Hospital and the Rochester Municipal Hospital during the winter of 1941-1942. The infants can be readily divided into the following two groups: infants with normal plasma and infants whose plasma clot resisted fibrinolysis. Although the former group is larger, the latter is of particular interest and is represented in tables 2 and 3.

TABLE 2.—*True Positive Reactions for Beta Streptococcic Antifibrinolysin in Blood of Newborn Infants*

Subject	Lysis Time in Hours			
	Cord Plasma	Cord Plasma + Normal Serum	Mother's Plasma	Cord Serum + Susceptible Plasma
G.	24	24	24	..
S.	24	20	3-18	..
L.	24	24	24	24
F.	24	24	12-24	24
M.	24	24	24	24
W.	6-20	6-20	2-2½	(*a*) 2 (*b*) 4-18

(*a*) and (*b*) represent two different plasmas.

TABLE 3.—*False Positive Reactions for Antifibrinolysin in Blood of Newborn Infants*

Subject	Lysis Time in Hours				
	Cord Plasma	Cord Plasma + Normal Serum	Cord Plasma + Euglobulin	Mother's Plasma	Cord Serum + Susceptible Plasma
S.	24	¼	..	..	..
K.	24	¼	..	..	..
O.	24	1	..	..	½
B.	24	1½	..	¾	..
V.	3¼ 17*	1 1*	..	¼	½
M.	5-12	(*a*) 4½ (*b*) 24	1½	1¼	(*c*) ½ (*d*) 2 (*e*) 24
W.	11	1½-2½	1½	2½	1
Wa.	24	¼	¼	¼	½

* These values were obtained from a repeat test done the following day on the same sample of plasma.
(*a*) and (*b*) represent two different normal serums.
(*c*), (*d*) and (*e*) represent three different normal plasmas.

Table 2 contains the results for 6 infants who appeared to have true positive reactions for antifibrinolysin. In each of their cases the cord plasma clot showed pronounced resistance to lysis, and the addition of normal adult serum did not alter the results significantly. As further

evidence for the presence of antibody, the cord serum of 3 of these infants conferred resistance to fibrinolysis on a normal susceptible plasma. The blood of the mother of each infant except subject W. also yielded an increase of antibody. The cord plasma of infant W. showed less resistance than did that of the others, and its cord serum conferred only slight resistance on each of 2 susceptible plasmas. The blood of this infant was considered to have a lower content of antifibrinolysin than that of the others, and, as might be expected, its mother had a low level of antibody.

The 8 newborn infants represented in table 3 appear to show false positive reactions for antifibrinolysin. In each case, the cord plasma clot had prolonged resistance to lysis, but when the test was repeated with the inclusion of normal adult serum, dissolution of the clot occurred promptly. Substitution of Milstone's "lytic factor" for the normal serum also resulted in prompt lysis in the 3 samples tested. Furthermore, the cord serums failed to confer resistance on normal susceptible plasma.

TABLE 4.—*Beta Streptococcic Antifibrinolysin of Newborn Infants*

Author	Number of Tests	Negative	False Positive	True Positive
Lippard and Wheeler [2]	28	14 (50%)	13 (46%)	1 (4%)
Boisvert [4]	6	0	6 (100%)	0
Lichty and Anderson	50	36 (72%)	8 (16%)	6 (12%)

The results of tests on subject M. did not entirely conform with those of the other subjects represented in table 3. The addition of normal adult serum did not effect a comparable reduction in lysis time of the cord plasma clot, although such a reduction did occur with use of "lytic factor," and the cord serum produced a wide variation of lysis times when mixed with 3 different susceptible plasmas. No satisfactory explanation was found for the inconsistent results in this case.

Table 4 gives a summary of the results of the present study and for the sake of comparison the results obtained by previous workers. Their results for newborn infants have been tentatively classified as true positive or false positive reactions on the basis of the presence or absence of antifibrinolysin in the mother's blood. This procedure seems justified, because in the present study a definite increase in antifibrinolysin was found in the blood of each mother whose infant showed a true positive reaction and it was not found in the blood of any mother of an infant with a "false positive" reaction. Tests were also performed on the maternal blood for each of 15 infants whose cord bloods gave negative reactions; in no case was an increased titer of antibody found.

COMMENT

If the hypothesis advanced by Milstone is correct, the cord blood of 36 newborn infants in the present study had sufficient euglobulin to effect prompt fibrinolysis. The data for the 6 infants comprising table 2 neither support nor refute this hypothesis, because the plasma of each had sufficient content of antifibrinolysin to resist lysis even when normal adult serum was added to the sample tested. The results in table 3 appear to support his explanation. They represent newborn infants whose plasma clots resisted lysis not by virtue of an increase in true antifibrinolysin but because some factor necessary for the mechanism of lysis was either diminished or absent. The addition of normal adult serum to the plasma tested supplied this substance, and in three instances the euglobulin "lytic factor" of Milstone served the same purpose.

In comparing the present results with those of previous workers, the high percentage of true positive reactions in the newborn infants might be attributed to the fact that the present study was conducted during the winter months, when infections with beta hemolytic streptococci were prevalent. No explanation was found for the low percentage of false positive reactions. When permitted to stand overnight, the plasma sample of subject V (table 3) showed an appreciable increase in resistance to fibrinolysis, but this effect was not found consistently in other specimens. The use of different strains of streptococci may account for the lack of closer agreement between the present results and those of other workers.

It is of some interest that in 3 of the newborn infants of Boisvert's series strongly positive antifibrinolysin reactions changed to negative by the tenth day of life. Since Lewis and Wells demonstrated that colostrum contains a large amount of euglobulin, it is conceivable that these infants received sufficient "lytic factor" by the tenth day to change a false positive reaction to a true negative.

SUMMARY AND CONCLUSIONS

Tests for beta streptococcic antifibrinolysin were performed on the blood of a series of 50 unselected newborn infants and 26 of their mothers. The blood of the infants was tested by both the standard technic and modifications of it involving the addition of normal adult serum or of a euglobulin fraction of normal adult serum.

On the basis of these tests, the reactions of the infants could be classified into the following three groups:

(*a*) Negative—plasma clot showing no resistance to lysis

(*b*) False positive—plasma clot resisting lysis in the routine test but not in the modified tests

(*c*) True positive—plasma clot resisting lysis in all tests.

That the blood of a newborn infant with a reaction in the third group possesses true antifibrinolysin was further confirmed by demonstrating increased antibody in its serum and in the blood of its mother.

The results of the present study indicate that when a mother possesses an increase of beta streptococcic antifibrinolysin the antibody is transmitted to her offspring by way of the placenta. If the mother does not have an increase of this antibody, the serum of her newborn child does not contain it, but a false positive reaction may be obtained with the plasma clot of this infant. This false positive reaction can be changed to a negative reaction by the addition of normal human serum or a euglobulin fraction of the serum.

At the time this paper was presented to the Society for Pediatric Research, Dr. Paul Boisvert reported essentially similar observations. These have been published in the *Proceedings of the Society for Experimental Biology and Medicine* (**49**:678, 1942).

Case Reports

PSEUDOHERMAPHRODITISM

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A recent advance in gynecology has been a better understanding of the problems of sexual development. True hermaphroditism is a condition in which one person possesses gonads containing microscopic elements resembling those of both the male and the female gonads. This condition is relatively rare. Twenty such cases with the diagnosis proved microscopically were collected by Young.[1] Most "hermaphrodites" are pseudohermaphrodites, that is, persons having either male or female gonads in association with various malformations of the external genitalia.

ETIOLOGY

The exact cause of such malformations is not entirely clear. According to Broster and Vines,[2] also quoted by Hamblen,[3] they are due to adrenal cortical hyperplasia or neoplasia during the fetal period. Adrenal cortical hyperplasia or neoplasia later in life also causes masculinization of the female, but with only moderate changes in the external genitalia (enlarged clitoris), hirsutism and male voice. Schiller [4] expressed the belief that change in sex may be congenital, resulting from a reversal of predominance of the chromosomes which determine genetic sex, or acquired, resulting from the hormonal influence of an ovarian tumor (arrhenoblastoma) or an adrenocortical tumor (hyperplasia or neoplasia).

CLASSIFICATION

Complicated morphologic classifications of pseudohermaphroditism have been prepared, based on anatomic variations of the genital malformations, but these are too cumbersome for practical use. Simpler morphologic classifications include male and female pseudohermaphroiditism, depending on which gonads are present in the subject.

Etiologically these sexual aberrations may be classified into (1) primary hermaphroditism and pseudohermaphroditism and (2) secon-

From the Negritos Hospital.

1. Young, H. H.: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases, Baltimore, Williams & Wilkins Company, 1937.
2. Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Co., Ltd., 1933.
3. Hamblen, E. C.: Endocrine Gynecology, Springfield, Ill., Charles C. Thomas, Publisher, 1939.
4. Schiller, W.: Internat. Clin. **3**:86-104, 1940.

dary pseudohermaphroditism. Primary hermaphroditism and pseudohermaphroditism may be due to what Schiller[4] called reversal of predominance of chromosomes which determine genetic sex. In the second type, secondary pseudohermaphroditism, there probably is no true hermaphroditism, because the sex chromosomes are not altered; instead, only the end organs (the genitalia) are altered.[5] These changes in the external genitalia are due to hormonal influences originating in an adrenal cortical tumor or ovarian tumor, such as a neoplasm of the adrenal cortex, an arrhenoblastoma or a hypernephroma of the ovary.[6] A dysgerminoma does not cause any genital changes, since it does not produce any known hormones, but such growth is found often in association with pseudohermaphroditism.[7]

Another classification which is beginning to play an important role in the treatment of these unfortunate persons is a psychiatric classification. Pseudohermaphroditic persons are grouped as male or female according to their training and the inclinations of their psychic make-up, regardless of their anatomic nature.[8] Thus, sometimes the sex the patient "chooses to live" is opposite to that which is shown anatomically.

Determination of the true anatomic sex of the patient is not always easy. Formerly laparotomy was performed routinely for this purpose. Now roentgenograms taken after pneumoperitoneum or after injection of air into the perirenal fat (Carrelli procedure) are preferred during the course of diagnosis.

However, with the advent of modern endocrinology, one may try an endocrine test, by injecting a gonadotropin into the patient, preferably before puberty, in order to see the reaction of the genitalia. One instance in which this was done is reported in the following case:

REPORT OF A CASE

A. G., aged 7½ years, came to the hospital in November 1940 because of a severe acute infectional gastroenteritis, from which she recovered promptly. At the same time a genital abnormality was noted.

History.—The patient was born spontaneously at full term, without difficulty, after a normal pregnancy. At birth the child looked normal physically, except that the mother thought that her genital parts "were swollen." Because of the absence of testicles and the presence of a small opening (urethral opening) at the base of the penis, she decided that the child was a girl, and it was brought up as such. At the age of 8 months the child had bilateral otitis media, from which she recovered in a short time. She walked with slight difficulty at the

5. Schiller, W.: Surg., Gynec. & Obst. **70**:773, 1940.

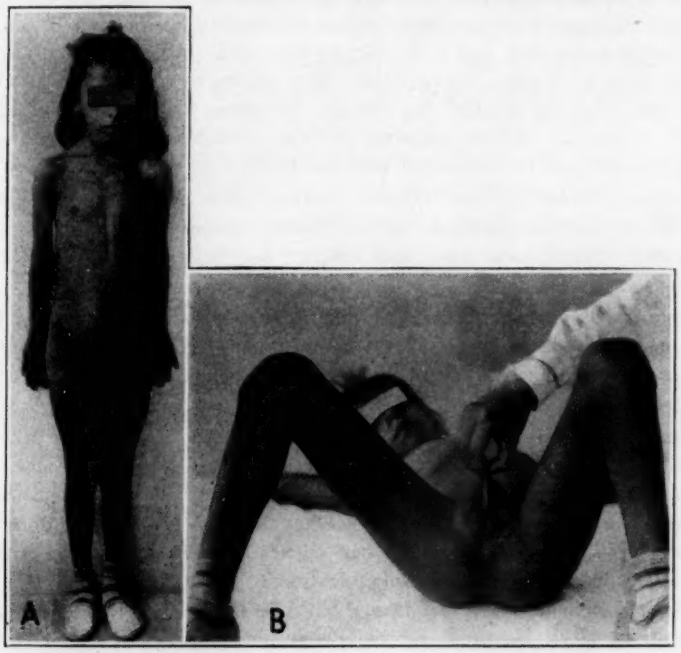
6. Novak, E.: Am. J. Obst. & Gynec. **36**:840, 1938.

7. (*a*) Taylor, H. C.: Am. J. Obst. & Gynec. **40**:566, 1940. (*b*) Meyer, R., cited by Karsner, H. T.: Tr. & Stud. Coll. Physicians, Philadelphia **7**:301, 1940. (*c*) Schiller.[5]

8. Greenhill, J. P., and Schmitz, H. E.: West. J. Surg. **48**:320, 1940.

age of 1½ years. She had one convulsion with loss of consciousness at the age of 1½ years; this convulsion was not associated with any known illness. She talked normally at the age of 3 years. The child had measles and whooping cough at the age of 3 years. Pubic hair began growing at the age of 4 years. Penile erection had never been noted by the parents, and no change of voice had been observed. She started to school at the age of 5 years, and she had progressed in her school work satisfactorily. Emotionally she had been stable and friendly and associated easily with other children; however, she had been rather sensitive about her genital parts. The parents stated that she "acted more like a boy."

Physical Examination.—The physical examination showed: temperature, 38.4 C. (101.1 F.); pulse rate, 140; respiratory rate, 40, and blood pressure, 105 systolic



A, photograph of the patient, showing the general development. *B*, the perineum. Note the female distribution of pubic hair, the attachment of the "penis" and the urethral opening.

and 70 diastolic. She was a well developed, fairly well nourished, bright-looking "girl," with loose flowing hair down to her shoulders. The features were slightly angular (fig., *A*). No hair was visible in the barba. She had slight pharyngitis; her voice was normal for a child. Otherwise the head and neck showed no abnormalities. The heart and lungs were normal. The breasts were normal for her age; there was no palpable breast tissue and no hair in that region. The abdomen showed hyperperistalsis of the intestines; otherwise it was normal. The femoral rings were small, without demonstrable bulging on straining or coughing. Testicles or spermatic cord was not felt in the inguinal canal. The extremities were normal except that the fourth toe of the left foot was about one-half the size of the corresponding toe of the right foot, which was normal.

The perineum showed abnormal genitalia (fig., *B*). There was a moderate amount of pubic hair in female distribution, 3 to 5 cm. in length. Where normally the clitoris should have been there was a penis-like structure 3 cm. in length and about 1.8 cm. in diameter held down by a thin membrane, which was attached to the "penis" from the frenulum down to its base; the other end of the membrane was attached to the midline of the perineum. The "penis" seemed to be made up only of the corpora cavernosa penis, with absence of the corpus cavernosum urethrae. The glans penis was complete except for the absence of a urinary meatus. Just below the attachment of the penile membrane to the perineum was the external urinary meatus (so proved by catheterization). There was no vaginal opening. On the sides of the perineum there were two structures which resembled the labia majora of a normal female child. No testicles could be palpated.

Rectal examination showed normal rectal structures. No prostate was palpable. At a depth of about 8 cm. in the rectum, a structure about the size of an almond was palpable inside the pelvis in the midline; this may have been a uterus. Adnexal structures were not palpable. By placing a rubber catheter in the bladder and palpating through the rectum, the entire length of the urethra was outlined; a prostate was not palpable, and the small mass on the midline previously mentioned was not connected with the bladder or the urethra.

Laboratory Examination.—Laboratory examination showed normal blood and urine. An intravenous pyelogram of the kidney showed a slight hydroureter on the left side. The kidneys were well outlined and in normal position; abnormal tumor masses were not seen.

Diagnosis.—Everything considered, the patient seemed to have been a cryptorchid male child with hypospadias who was being brought up as a girl. The indications that this patient might be a girl were the small mass in the midline of the pelvis and the female distribution of the pubic hair.

Therapy and Progress.—Since the mother was eager to know the true sex of the child and since laparotomy carries a certain risk, especially in absence of a demonstrable abdominal tumor, it was decided to test the child's genital apparatus with a gonadotropin. Accordingly 5,000 rat units of chorionic gonadotropin (antuitrin S) was given intramuscularly in 500 rat unit doses twice weekly for five weeks. The penis was carefully measured. It was noted that it increased from 3 to 4.1 cm. in length and from 1.8 to 2.4 cm. in diameter. This indicated a moderate increase. No penile erections were noted during the course of therapy. Palpation of the internal organs showed the same conditions as before. No change in size was noted.

The plan proposed for further treatment of this child is to wait until puberty so that the psychic makeup may assert itself fully. Plastic operations will then be carried out to satisfy the natural inclinations of the patient. In the meantime she will be carefully followed up, with particular attention to appearance of abdominal or perirenal tumors.

COMMENT

Accurate diagnosis from the standpoint of causation is extremely important in cases of pseudohermaphroditism in regard to treatment and ultimate prognosis of the patient.

Probably in a good many pseudohermaphrodites the abnormality results from reversal of sex chromosomes. This group cannot be distinguished except by exclusion. Therapy for this group is reduced to plastic operation on the external genitals to make them fit the sex the patient wishes to choose.

Pseudohermaphroditism resulting from pathologic conditions of the adrenal may be due to a benign hyperplasia or adenoma of the cortex or to a malignant growth of the cortex (hypernephroma). The androgenic cone of the adrenals, which exists only during the fetal period and the first year of extrauterine life, is said to give rise to growths that produce genital changes.[9] There are no genital changes in association with neoplasia of the medulla of the adrenal. Such a tumor should be removed surgically if possible. If a malignant growth has developed and is too far advanced for surgical intervention, radiation therapy should be used as soon as possible.

Meyer[7b] found that in 56 per cent of 48 cases of dysgerminoma of the ovary there was some degree of pseudohermaphroditism. The incidence of cancer in this type of tumor is reported variously by different authors. Fördel[10] noted that in a sufficient length of time 68 per cent of 55 patients observed had metastases. In other words, malignant degeneration of a dysgerminoma is possible. Treatment should be surgical intervention or radiation or both if necessary. Plastic operation on the external genitals should be carried out to satisfy the patient.

Arrhenoblastoma and hypernephroma (also called hypernephroid tumors) of the ovary are masculinizing and are extremely rare.[6] The incidence of malignancy in these tumors is not known. However, surgical eradication of them is the preferred method of therapy.

In general, pseudohermaphrodites should be studied carefully, and a laparotomy should be performed if there is indication of a tumor in the pelvic cavity or the region of the adrenals. If there is no demonstrable tumor, one can afford merely to treat the external genitalia by a plastic operation to suit the psyche of the patient.

The biologic test used in the case reported here, injection of a gonadotropin into the patient and observation of the reaction of the external and internal genitalia, is based on the fact that when human chorionic gonadotropin is injected into immature male monkeys it stimulates the interstitial cells of the testes and leads to production of androgen.[11] The androgen causes an increase in the size of the penis, which can be observed externally. Clinically this can be seen in the treatment of

9. Grollman, A.: The Adrenals, Baltimore, Williams & Wilkins Company, 1936.

10. Fördel, V.: Arch. f. Gynäk. **165**:392, 1938.

11. Engle, E. T., and Levin, L.: Gonadotropins of Anterior Lobe of Pituitary and of Chorionic Tissue, J. A. M. A. **116**:47 (Jan. 4) 1941.

the cryptorchid human male, in whom the testicles often descend.[12] Injection of human chorionic gonadotropin into a human female does not produce any notable changes in the ovaries or endometrium.[11] Therefore, when human chorionic gonadotropin is injected into a pseudohermaphrodite whose sex is in question, if the gonads are testes they may descend when cryptorchid and the penis may grow in size. On the other hand, if the gonads are ovaries no definite reaction will be noted. Use of pituitary gonadotropin would, of course, be better when the subject is suspected to be a female, since it has a definite effect on the ovaries (production of estrogen and increase in size of the uterus and breasts).

SUMMARY AND CONCLUSIONS

Pseudohermaphrodites should be studied carefully, and if these studies reveal a tumor in the pelvic cavity or around the adrenals, a laparotomy should be performed to extirpate the growth, especially if it is suspected to be an adrenal neoplasm or a dysgerminoma of the ovary, as such growths may become malignant.

The external genitalia should be treated with a plastic operation to suit the psyche and natural inclinations of the patient, so as to help "him" or "her" to be better adjusted to the sex "he" or "she" wishes to live.

A biologic test with gonadotropin is suggested as an aid for determining the functional nature of the gonads of patients whose sex is not apparent.

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12. (*a*) Zelson, C.: J. Pediat. **14**:452, 1939. (*b*) Thompson, W. O., and Heckel, N. H.: Undescended Testes: Present Status of Glandular Treatment, J. A. M. A. **112**:397 (Feb. 4) 1939.

TRANSITORY HEMIPLEGIA ASSOCIATED WITH HYPOGLYCEMIA IN A DIABETIC CHILD WITH CONGENITAL HEART DISEASE

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AND
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A 9 year old girl with congenital heart disease who was intensely cyanosed acquired a right hemiplegia due to a cerebral thrombus. She recovered in about three months. Two years later she became diabetic and was given insulin; during a hypoglycemic reaction a right hemiplegia again developed. Because transitory focal cerebral symptoms may occur as a manifestation of insulin shock (Ford,[1] Root [2] and Woodyatt [3]) and closely simulate cerebral vascular accidents, this case is reported in detail.

REPORT OF A CASE

M. Y., a 4 year old girl, was first seen at Mount Sinai Hospital in 1935. She had been cyanosed at intervals since birth. A rough systolic murmur was heard over most of the precordium, and a diagnosis of congenital heart disease was made.

By 1937, when she was 6 years old, the cyanosis had become constant. The cardiac condition was diagnosed as the tetralogy of Fallot. The red blood cell count was 8,700,000 per cubic millimeter.

In February 1939, when she was 8 years of age, some irritability, difficulty in grasping objects with the right hand, a right-sided limp and thick, slurred speech followed by aphasia were noted. The impression of the consulting neurologist, Dr. Beeber, at that time was that she had had a vascular lesion, probably thrombotic, in the left capsular and thalamic areas. Her muscle power returned gradually, and three months later there were no residua. The urine was sugar free; hence there was as yet no evidence of diabetes mellitus.

In February 1941, when she was 10 years of age, following tonsillitis and cervical adenitis, polydipsia, polyuria and pruritus developed, and she lost weight. She was admitted to the hospital on February 22 in mild ketosis. The urine contained a large amount of dextrose and acetone. The blood sugar content was 582 mg. per hundred cubic centimeters; the carbon dioxide-combining power of the serum, 26 volumes per cent. She was given insulin and a restricted diet. The glycosuria disappeared. After ten days the urine was free of sugar and insulin

From the Pediatric Service, Mount Sinai Hospital.

1. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Springfield, Ill., Charles C. Thomas, Publisher, 1937, p. 602.

2. (*a*) Root, H. F.: Personal communication to the authors. (*b*) Root, H. F., and Styron, C. W.: Insulin Hypoglycemia and Vascular Accidents in Diabetes Mellitus, J. Mt. Sinai Hosp. **8**:953, 1942.

3. Woodyatt, R. T.: Diabetes Mellitus, in Cecil, R.: Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1940, p. 697.

therapy was stopped. The fasting blood sugar value was 75 mg. per hundred cubic centimeters, but the dextrose tolerance curve gave high blood sugar values (reaching 270 mg. per hundred cubic centimeters), indicating a decreased tolerance for dextrose and confirming the impression of diabetes mellitus. In view of the history of a previous cerebral accident, the possibility that a fresh intracranial hemorrhage had caused the glycosuria was entertained. A lumbar puncture revealed normal spinal fluid.

She was placed on a restricted carbohydrate diet without insulin, and was sent home, only to return to the hospital within two months (April 1941) with recurrent symptoms of diabetes mellitus. The glycosuria was easily controlled, but it was felt that she could no longer be successfully treated without insulin. Therefore, she was given a daily dose of 10 units of protamine zinc insulin before breakfast. The mother was instructed in diabetic management,[4] and the child was seen at regular intervals in the outpatient department.

In October and November 1941, because glycosuria recurred, the dose of protamine zinc insulin was gradually increased to 30 units daily. However, in spite of glycosuria during the daytime on several occasions, she was drowsy when awakened in the early morning and required carbohydrate before becoming fully conscious.

In February 1942, when 11 years old, the child acquired an infection of the upper respiratory tract. Early on the morning of February 5, the mother was attracted by the child's peculiar "yawning" type of breathing and restlessness. She could not be aroused. Approximately six hours later, and about thirty hours after receiving 30 units of protamine zinc insulin, she arrived at the hospital for treatment.

The physical examination on admission showed: temperature, 103 F.; pulse rate, 112 per minute; respiratory rate, 24 per minute, and blood pressure, 85 systolic and 60 diastolic. The patient was lying on the left side and was cyanotic, flushed and stuporous. Whenever she was disturbed, she made many movements of rejection with the left arm and leg. There were movements of the right extremities only as a component of the movements of the whole body. The eyes deviated to the left and did not move beyond the midline. There were no retinal hemorrhages. The neck was not held rigidly. Both knee jerks were hyperactive. The right Babinski reflex was elicited; the response to pinprick everywhere was slower on the right side of the body. The skin was warm and dry. A loud basal systolic murmur and a rough second aortic sound were heard over the precordium. The odor of acetone was not detected on the breath. The throat was injected. The urine was free of sugar and acetone. The diagnosis of either a recurrent thrombosis or a severe hypoglycemic reaction was made.

With the latter possibility in mind, and especially since the urine was free of sugar, the patient was given 25 cc. of 50 per cent dextrose solution intravenously. This aroused her slightly, but she remained semistuporous for some hours. The blood sugar level determined before the administration of dextrose was reported as only 40 mg. per hundred cubic centimeters. The red blood cell count was 9,300,000 per cubic millimeter. Inasmuch as her sucking reflex was good, she was given liquid nourishment through a rubber-tipped syringe. After she had retained some fluid, she was given 10 units of protamine zinc insulin. That evening, about eighteen hours after the onset of the attack, she seemed more alert and moved her right arm slightly. During the night she had glycosuria, and the

4. Fischer, A. E.: A Diabetic Primer for Children, ed. 2, New York, The Author, 1938.

following morning the fasting blood sugar was 105 mg. per hundred cubic centimeters. She was afebrile. That evening, approximately thirty-six hours after the onset of the reaction, she was completely oriented, talked and moved all extremities equally well. There was no longer any evidence of extraocular paralysis or a positive Babinski reflex. Five days later, Dr. Needles, the consulting neurologist, reported no abnormal findings. Subsequently, an electroencephalogram, taken with the patient fasting, gave a record which was interpreted by Dr. H. Strauss as characteristic of "diffuse cerebral dysfunction from extracerebral cause; i. e., anoxemia, fever or exogenous intoxication."

During this stay in the hospital she was given regular insulin instead of protamine zinc insulin, and at the time of discharge, on March 23, she was receiving a diet of 170 Gm. of carbohydrate, 50 Gm. of protein and 55 Gm. of fat, with 15 units of regular insulin at 7 a. m. and 9 units at 7 p. m. With this regimen the urine was usually sugar free.

After the episode which has been presented in detail, there was another slight reaction. On April 3, 1942, because she had been having glycosuria, the mother had increased the 7 p. m. dose of insulin to 10 units. That evening the child refused milk, which was always given at bedtime. During the early hours of the morning of April 4, the child once again acted queerly and had sighing respirations. The mother was unable to arouse her and therefore forced her to take some orange juice. Although most of it was vomited, she awakened and complained of a left-sided headache. The urine was free of sugar at that time. After further forcing of orange juice and delay in giving the morning dose of insulin, the child became more alert. When she was seen one week later, she did not have paralysis and her diabetes was under control.

COMMENT

Of especial interest was the episode which occurred in February 1942. The differential diagnosis of the symptom complex which this child presented at that time lay between a recurrent cerebral thrombosis or angiospasm and a severe insulin reaction. Symptoms of both were present.

In favor of a recurrent thrombus were the dry skin, the normal blood pressure, the intense polycythemia, the history of a previous cerebral thrombosis and the rather complete right hemiplegia. The hour of onset suggested hypoglycemia as the cause, for it corresponded to the period of maximum effect of protamine zinc insulin. We treated her for hypoglycemia, but she responded only momentarily to an intravenous injection of dextrose. It is well known that in severe insulin shock due to protamine zinc insulin the response to intravenously administered dextrose may be slow and incomplete. When the blood sugar level on her admission to the hospital was found to be only 40 mg. per hundred cubic centimeters, it became apparent that at least part of the stupor was due to hypoglycemia. The administration of dextrose was therefore continued. The subsequent course of the child's symptoms showed how large a part hypoglycemia actually played. In eighteen hours, coincident with the rise in the blood sugar level, the child recovered consciousness,

and in two days the hemiplegia had cleared completely. This was in contrast to the cerebral episode two years previously, following which complete recovery took place only after several months.

We have considered it probable that the previous cerebral thrombus had left a "locus minoris resistentiae," and it is likely that the threshold of response in the brain to insulin might be lowered at the site of an antecedent disease process. In this way one might explain the severe focal cerebral manifestations produced by a hypoglycemic reaction. Such an effect would be more readily demonstrable in a patient with polycythemia, in whom the decreased blood flow and the bradycardia which occur during hypoglycemia were accentuated and tended to increase cerebral anoxia.

This patient is being treated now with regular insulin, because of the difficulty in regulating her diabetes and because it is well known that hypoglycemic reactions secondary to regular insulin usually clear up more promptly after the administration of dextrose than do reactions secondary to protamine zinc insulin. Furthermore, prolonged hypoglycemic reactions may permanently damage the brain. Instances of damage to the brain have been reported recently by Allan and Crommelin [5] and by Root and Styron.[2b] Himwich [6] pointed out the deleterious sequence of events in the central nervous system following hypoglycemia.

SUMMARY

During a hypoglycemic insulin reaction a child with congenital heart disease and diabetes mellitus presented a clinical picture which closely simulated the hemiplegia due to a cerebral thrombosis which she had had two years previously. The importance of recognizing similar insulin reactions is emphasized.

73 East Ninetieth Street.

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5. Allan, F. N., and Crommelin, R. M.: Cerebral Damage from Insulin "Shock": Hemiplegia, Aphasia and Epileptic Seizures for Fifteen Months, J. A. M. A. **118**:373 (Jan. 31) 1942.

6. Himwich, H. E.: An Interpretation of the Symptoms of Hypoglycemia, in Fundamental Concepts in the Treatment of Diabetes Mellitus and Its Complications, New York, New York Diabetes Association, 1942, no. 21.

SUBACUTE BACTERIAL ENDOCARDITIS DUE TO HEMOLYTIC STREPTOCOCCI OF LANCEFIELD GROUP G

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Developments in the field of chemotherapy have aroused an increased interest in a more exact bacteriologic differentiation of the various groups of streptococci in order to understand the varied responses of patients suffering from streptococcic infections to sulfanilamide and its derivatives. By means of a precipitation test devised by Lancefield [1] the hemolytic streptococci may be divided into nine groups, which are designated by letters of the alphabet. The great majority of virulent human streptococcic infections are caused by members of group A. Organisms of this group commonly form toxic substances, such as hemolysin, fibrinolysin, erythrogenic toxin and leukocidin. Scarlet fever and erysipelas are caused by hemolytic streptococci belonging to group A. The remaining groups of hemolytic streptococci, known as B, C, D, E, F, G, H and K, may cause infection occasionally in man, but such infection is generally mild. Many of them are animal streptococci.

REPORT OF A CASE

A girl, 8 years old, was admitted to the clinic on June 25, 1941. When she was an infant, her parents had been told that she had congenital heart disease. On May 10 she had lobar pneumonia. At that time, it was found that her tonsils were infected, that she had a loud murmur and a thrill over the precordium and that a blood culture showed hemolytic streptococci. She had several transfusions, and she was treated with sulfathiazole, 10 grains (0.65 Gm.) every four hours. On admission to the clinic she was thin and pale but cheerful and not at all uncomfortable. The blood pressure was 100 mm. of mercury systolic and 62 diastolic; the pulse rate was 108, and the temperature was 99.8 F. There were an obvious systolic thrill in the fourth and fifth interspaces on the left and a loud harsh systolic murmur heard over the left side of the chest. The lungs were clear. The remainder of the examination gave essentially normal results. The temperature was 103.7 F. on admission, and it fluctuated within twenty-four hours from 98 to 104 F. The blood culture showed hemolytic streptococci.

From the Section on Pediatrics and the Section on Bacteriology, Mayo Clinic.

1. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571-595 (April) 1933.

This patient was treated at first with sulfanilamide (table 1). She had up to 100 grains (6.5 Gm.) daily for seventeen days. The temperature varied from 98 to 104 F. The level of the sulfanilamide in the blood reached 14.6 mg. per hundred cubic centimeters, and the blood culture showed 90 colonies per cubic centimeter of blood. During the next period of seventeen days the patient received up to 100 grains (6.5 Gm.) daily of sulfathiazole, and her temperature varied from 98 to 102.5 F. The blood culture showed still more organisms than it had with the sulfanilamide. During the next period of ten days she received sulfadiazine up to 105 grains (6.8 Gm.) daily, and the temperature remained between 97.5 and 101 F. Blood cultures still showed as many as 80 colonies per cubic centimeter of blood. During the fourth period of eleven days the patient again received sulfanilamide combined with vironamin,[1a] which is an organic preparation supposed to reduce toxicity. This was perhaps the best period. The temperature remained between 98 and 99 F., reaching 101 F. only once. The blood culture during this treatment showed more organisms per cubic centimeter than at any other time.

TABLE 1.—*Course of Septicemia During Treatment with Drugs*

Dates, 1941	Medication	Temperature, F.	Blood Level of Drug, Mg. per 100 Cc.	Blood Culture Colonies per Cc.	Urine
6/27 to 7/14	Sulfanilamide, 100 grains (6.5 Gm.) daily	98 to 104	14.6	90	Entirely normal
7/17 to 8/3	Sulfathiazole, 100 grains (6.5 Gm.) daily	98 to 102.5	8 to 11	248	Sulfathiazole crystals +; otherwise normal
8/3 to 8/13	Sulfadiazine, 105 grains (6.8 Gm.) daily	97.5 to 101	17 to 25.8	80	Sulfadiazine crystals +; otherwise normal
8/19 to 8/30	Sulfanilamide, 100 grains (6.5 Gm.) daily	98 to 99	23 to 40	Innumerable (3 cultures)	
	Vironamin, 200 grains (13 Gm.) daily	(101 once)			
8/30 to 9/12	.....	98 to 102	.....	.....	Albuminuria* 2+; erythrocyturia* 1 to 4; casts

* On a basis of 1 to 4.

The patient stayed in the hospital for three months. All this time she seemed reasonably well, in spite of the blood cultures. It was suspected that this might be an unusual type of streptococcus, and it was identified further as a streptococcus of the Lancefield group G. Two weeks before her dismissal enlargement of the liver and spleen developed, with edema of the dependent parts, albuminuria and hematuria. During administration of the different drugs the concentration of hemoglobin fell on several occasions to a level of 5 or 6 Gm. per hundred cubic centimeters of blood. At these times the medication was stopped, a transfusion was given and the hemoglobin returned to a reasonable level. The leukocytes varied from 7,000 to about 14,000 to 20,000 per cubic millimeter of blood. The sedimentation rates were at various times from 90 to 125 mm. Roentgenograms of the chest showed obvious cardiac enlargement and some degree of congestion. The patient was dismissed from the clinic on September 12 and died at home on October 7. Necropsy was not permitted.

1a. Vironamin is made up of calcium gluconate 20 per cent, aminoacetic acid 40 per cent, calcium glucuronate 10 per cent, l-cystine 10 per cent, ascorbic acid 10 per cent, choline chloride 1.5 per cent and starch, sugar and talc to make 100 per cent.

COMMENT

The organism found in cultures of the blood of this patient was a group G hemolytic streptococcus. On blood agar plates it formed large zones of beta hemolysis indistinguishable from those of colonies of group A hemolytic streptococci. The fact that it was found in such large numbers in the blood stream over such a long period with the patient still surviving was inconsistent with the presence of group A hemolytic streptococci, the usual type causing septicemia in man.

Table 2 is a summary of the cases in the literature in which hemolytic streptococci of group G have been isolated from the blood. Lancefield and Hare [2] reported 1 case. In this case the patient had Staphylococcus aureus as well as hemolytic streptococci of the Lancefield group G in the blood stream. In 2 cases reported by Colebrook and Purdie [3]

TABLE 2.—*Infections with Type G Hemolytic Streptococci*

	Type of Case	Organisms	Result
Lancefield and Hare, 1935 1 case	Septicemia	Staphylococcus aureus Hemolytic streptococci G	Died
Colebrook and Purdie, 1937			
1 case	Septicemia following severe trauma	Hemolytic streptococci G	Died; hemorrhage on third day
1 case	Septicemia	Anaerobic streptococci Bacilli type ? Hemolytic streptococci G	Died; extensive thrombophlebitis and pulmonary infarction
Pomales-Lebrón, 1940 2 cases	Septicemia	Hemolytic streptococci G	1. Died; agranulocytosis 2. Died; puerperal sepsis

in which hemolytic streptococci of the Lancefield group G was recovered, 1 patient died of hemorrhage on the third day and the other died with extensive thrombophlebitis and pulmonary infarction. This last patient had, in addition to the group G streptococci, anaerobic streptococci and a bacillus of an unidentified type. Pomales-Lebrón [4] reported 2 fatal cases of septicemia from Puerto Rico. One of the patients had agranulocytosis and the other puerperal sepsis.

Group G hemolytic streptococci are found most commonly in the normal human throat, vagina or feces and in normal animal throats.

2. Lancefield, R. C., and Hare, R.: The Serological Differentiation of Pathogenic and Non-Pathogenic Strains of Hemolytic Streptococci from Parturient Women, J. Exper. Med. **61**:335-349 (March) 1935.

3. Colebrook, L., and Purdie, A. W.: Treatment of One Hundred and Six Cases of Puerperal Fever by Sulphanilamide, Lancet **2**:1237-1242 (Nov. 27) 1937.

4. Pomales-Lebrón, A.: A Study of Hemolytic Streptococci as Found in the Tropical Island of Puerto Rico, Puerto Rico J. Pub. Health & Trop. Med. **16**:67-133 (Sept.) 1940.

They have also been isolated occasionally from mild sore throats in human beings, but rarely have they been known to cause dangerous infections. They rarely produce erythrogenic toxin or fibrinolysin. Production of fibrinolysin, a substance which rapidly dissolves the clotted fibrin of normal human plasma, is a regular property of streptococci causing severe infections. The group G strain isolated from the patient under discussion was not found to produce fibrinolysin. It was not virulent for mice. With these findings the continued presence of large numbers of this organism in the blood of the patient without great evidence of a toxic state becomes understandable. The organism fermented glycerol.

Reports in the literature indicate that hemolytic streptococci are rather regularly sensitive to the action of sulfanilamide and its derivatives, with the exception of those belonging to group D (the enterococci) and certain members of group G. The action of sulfanilamide in vitro was tested on several group G strains, including the one from the patient, and on several group A strains, the liver infusion medium of MacLeod,[5] which is free of sulfonamide inhibitors, being used and defibrinated human blood also being employed as a medium. It took twice as much sulfanilamide to inhibit growth of the strain isolated from the patient as was necessary to inhibit growth of the other group G strains. Group A strains, however, tended to be naturally more resistant to sulfanilamide than any of the group G strains. It appears that the failure of sulfanilamide and its derivatives to sterilize the blood stream of the patient was due to the inherent or acquired resistance of the organism to the drug and to the probable presence of a focus of infection in a valve of the patient's heart.

Mayo Clinic.

5. MacLeod, C. M.: The Inhibition of the Bacteriostatic Action of Sulfonamide Drugs by Substances of Animal and Bacterial Origin, J. Exper. Med. **72**:217-232 (Sept.) 1940.

Progress in Pediatrics

INTRACTABLE HYPOPHOSPHATEMIC RICKETS WITH RENAL GLYCOSURIA AND ACIDOSIS (THE FANCONI SYNDROME)

REPORT OF A CASE IN WHICH INCREASED URINARY ORGANIC ACIDS WERE DETECTED AND IDENTIFIED, WITH A REVIEW OF THE LITERATURE

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Severe rickets of the familiar variety, due to dearth of sunlight or lack of proper food, has virtually disappeared from communities which have adopted the regular prophylactic use of vitamin D. This noteworthy development has served to give prominence to the less common species which are causally dependent on intrinsic peculiarities of metabolism.

Boyd [1] has properly stressed the diversity of clinical aspect which characterizes many of the examples of metabolic, or endogenous, rickets. This feature is undeniably worthy of emphasis. However, it is not warranted to conclude that lack of obvious or complete congruence among the reported cases invariably denotes that they are fundamentally dissimilar. In many instances the discordance is more apparent than real, reflecting chiefly the superficial level to which medical investigation is often necessarily restricted. The literature abounds in cases of endogenous rickets which for want of critical

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1. (*a*) Boyd, J. D.: An Unusual Syndrome Associated with Rickets, Am. J. Dis. Child. **33**:539 (March) 1927; (*b*) Endogenous Rickets, Proc. Soc. Exper. Biol. & Med. **26**:181 (Dec.) 1928. (*c*) Boyd, J. D., and Stearns, G.: Types of Disturbances of Mineral Metabolism Associated with Bone Dystrophies, ibid. **27**: 241 (Dec.) 1929. (*d*) Boyd, J. D.: Chronic Acidosis Secondary to Ureteral Transplantation, Am. J. Dis. Child. **42**:366 (Aug.) 1931. (*e*) Boyd, J. D., and Stearns, G.: Late Rickets Resembling the Fanconi Syndrome, ibid. **61**:1012 (May) 1941.

information cannot be exactly interpreted: Of these the reports of Ullrich,[2] Schlesinger,[3] Bornscheuer[4] and Stechele[5] provide examples.

The state of the subject remains confused; it is, however, not entirely chaotic. Discriminating inquiry has revealed several common denominators which, while they do not always point directly to causation and pathogenesis, do serve to segregate certain cases into groups and thus to define features which require further study.

One such species is that which has been designated refractory or essential hypophosphatemic rickets.[6] In most aspects this type resembles ordinary infantile rickets. The most distinctive feature is that, while the rachitic process is highly resistant to treatment and displays a strong disposition to persist into childhood, it can be controlled by the continued administration of extraordinary doses of vitamin D, approximating 100,000 U. S. P. units daily.

The fault of metabolism which is responsible for this type of rickets has not been precisely localized. However, other species have been described in which the defect of mineralization is assignable with greater or less confidence to a fundamental flaw of function of an individual viscus: Celiac rickets, for example, with its somewhat debatable connotation of pancreatic insufficiency,[7] has been much discussed. While hepatic rickets[8] has not yet been verified[9] as an authentic

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2. Ullrich, O.: Versager der Rachitistherapie und Tierrachitis, München. med. Wchnschr. **76**:1433 (Aug. 23) 1929.

3. Schlesinger, B.: Renal Dwarfism and Rickets, Proc. Roy. Soc. Med. **25**: 10 (Nov.) 1931.

4. Bornscheuer, P.: Ein Fall von endogener, gegen D-Vitamin und Licht resistenter, perennierender Rachitis, Ztschr. f. Kinderh. **51**:56, 1931.

5. Stechele, U.: Ueber das Krankheitsbild der sogenannten renalen Rachitis, Ztschr. f. Kinderh. **61**:448, 1939.

6. (*a*) Stearns, G.; Oelke, M. J., and Boyd, J. D.: Mineral Metabolism in Late Rickets, Am. J. Dis. Child. **42**:88 (July) 1931. (*b*) Stearns, G., and Boyd, J. D.: The Healing of Rickets Coincident with Low Serum Inorganic Phosphorus, J. Clin. Investigation **10**:591 (Aug.) 1931. (*c*) Highman, W. J., Jr., and Hamilton, B.: Calcium and Phosphorus Metabolism in a Case of Intractable Rickets, J. Pediat. **9**:56 (July) 1936. (*d*) Albright, F.; Butler, A. M., and Bloomberg, E.: Rickets Resistant to Vitamin D Therapy, Am. J. Dis. Child. **54**:529 (Sept.) 1937. (*e*) Bakwin, H.; Bodansky, O., and Schorr, R.: Refractory Rickets, ibid. **59**:560 (March) 1940. (*f*) Christensen, J. F.: Three Familial Cases of Atypical Late Rickets, Acta pædiat. **28**:247, 1941.

7. Parsons, L. G.: The Bone Changes Occurring in Renal and Celiac Infantilism and Their Relationship to Rickets: Part II. Celiac Rickets, Arch. Dis. Childhood **2**:198, 1927.

8. Gerstenberger, H. J.: Rachitis Hepatica, Monatschr. f. Kinderh. **56**:217, 1933.

9. (*a*) Thoenes, F., and Gruson, W.: Zur Frage der "Rachitis hepatica," Monatschr. f. Kinderh. **67**:134, 1936. (*b*) Eliot, M. M., and Park, E. A.: Rickets, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Co., Inc., 1938, vol. 1, chap. 36.

clinical entity, the likelihood of its occurrence is supported by the results of extensive experimentation.[10] Of the several varieties, classic renal rickets,[11] otherwise and better known as renal hyperparathyroidism,[12] is the most familiar. Both because of historical priority of description and because of its frequency, it is the best known example of defective calcification of the growing skeleton caused by disordered function of a single organ.

The pathologic structure of the kidneys in renal rickets implies reduced efficiency of all functional elements of the nephron. However, elevation of nonprotein nitrogen and of inorganic phosphorus in the blood lends greater prominence to the diminished amount of the glomerular filtrate than to the consequences of defective tubular excretion and resorption. In fact, the conviction that nephropathic rickets is consistently signalized by accumulation of catabolites in the body fluids has so completely dominated clinical thinking that it has been customary to ignore the complicity of the kidneys in cases in which this feature has not been present. Until recently little attention seems to have been paid to the possibility that defect of one or more of the resorptive functions of the renal tubular epithelium if unaccompanied by commensurate restriction of filtration might yield an opposite result, namely, reduction, rather than retention, of metabolites in the blood. To the best of our knowledge, Fanconi [13] was the first to apply this hypothesis to the interpretation of a medical problem. Amplified to include the concept of defective tubular secretion, it supplies a helpful interpretation of the cases of hypophosphatemic, hyperchloremic rickets with nephrocalcinosis and reduced urinary ammonia observed by But-

10. Heymann, W.: Metabolism and Mode of Action of Vitamin D: IV. Importance of Bile in the Absorption and Excretion of Vitamin D, J. Biol. Chem. **122**:249 (Dec.) 1937.

11. Mitchell, A. G.: Nephrosclerosis (Chronic Interstitial Nephritis) in Childhood, with Special Reference to Renal Rickets, Am. J. Dis. Child. **40**:101 (July); 345 (Aug.) 1930.

12. Park, E. A., and Eliot, M. M.: Renal Hyperparathyroidism with Osteoporosis (Osteitis) Fibrosa Cystica, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Co., Inc., 1938, vol. 3, chap. 29.

13. (*a*) Fanconi, G.: Die nicht diabetischen Glykosurien und Hyperglykämien des älteren Kindes, Jahrb. f. Kinderh. **133**:257, 1931; (*b*) Der nephrotisch-glykosurische Zwergwuchs mit hypophosphatämischer Rachitis, Deutsche med. Wchnschr. **62**:1169 (July 17) 1936; (*c*) Der frühinfantile nephrotisch-glykosurische Zwergwuchs mit hypophosphatämischer Rachitis, Jahrb. f. Kinderh. **147**:299, 1936. (*d*) Sturzenegger, H.: Zur pathologischen Anatomie des frühinfantilen nephrotisch-glykosurischen Zwergwuchses mit hypophosphatämischer Rachitis (Fanconi); Ann. pædiat. **153**:1, 1939.

ler [14] and studied extensively by Albright and his co-workers.[15] It also provides an explanation of the case recently described by Boyd,[16] of which hypophosphatemia, hypochloremia and greatly reduced plasma cation were the critical features.

Fanconi's hypothesis has merit outside of the field of rickets. Hypocalcemic tetany without rickets can result from selective inability to resorb calcium from the glomerular filtrate. Such, at least, is the essence of the argument advanced by one of us [17] to throw light on the obscure features of a unique case of nephrocalcinosis. Hartmann [18] has postulated a defect of resorption involving bicarbonate to account for the pathogenesis of a single example of recurrent acidosis. As a final illustration of the novel syndromes which can result from restricted defect of filtration, we wish to cite the case of a child now under observation, whose only manifestation of diffuse calcification of the kidneys is diabetes insipidus of the type that is not moderated by injections of pitressin. Judged by their behavior during clearance tests, the boy's kidneys are normally efficient with respect to the disposal of endogenous and exogenous creatinine, sodium, chlorine, phosphorus, urea, dextrose and amino acids and they produce ammonia in physiologic amounts; the deduction is that the lesion is limited to defective tubular resorption of water. The presence of shadows of calcium density within the renal parenchyma and the lack of response to appropriate doses of an extract containing the posterior pituitary antidiuretic principle (pitressin) support the idea that this is diabetes insipidus of renal tubular origin rather than of diencephalic origin.

The concept of tubular renal rickets as opposed to glomerular renal rickets was introduced by Fanconi to account for the pathogenesis of several examples of intractable normoazotemic, hypophosphatemic rickets accompanied by chronic acidosis and renal glycosuria. This constellation had been observed before, but no well grounded interpretation had been offered. Attesting the originality and importance of

14. Butler, A. M.; Wilson, J. L., and Farber, S.: Dehydration and Acidosis with Calcification at Renal Tubules, J. Pediat. **8**:489 (April) 1936.

15. Albright, F.; Consolazio, W. V.; Coombs, F. S.; Sulkowitch, H. W., and Talbott, J. H.: Metabolic Studies and Therapy in a Case of Nephrocalcinosis with Rickets and Dwarfism, Bull. Johns Hopkins Hosp. **66**:7 (Jan.) 1940.

16. (*a*) Boyd, J. D., and Stearns, G.: Chronic Acidosis as a Concomitant of Late Rickets, Am. J. Dis. Child. **62**:463 (Aug.) 1941; (*b*) Concomitance of Chronic Acidosis with Late Rickets, ibid. **64**:594 (Oct.) 1942.

17. McCune, D. J., and Pray, L. G.: Nephrocalcinosis with Chronic Tetany, Am. J. Dis. Child. **60**:993 (Oct.) 1940.

18. Hartmann, A. F.: Clinical Studies in Acidosis and Alkalosis: Use and Abuse of Alkali in States of Bicarbonate Deficiency Due to Renal Acidosis and Sulfanilamide Alkalosis, Ann. Int. Med. **13**:940 (Dec.) 1939.

his contribution, Fanconi's name is properly linked with the complex. Inasmuch as it is clearly symptomatic of more than one basic cause, we have avoided the somewhat too definitive term Fanconi's type of rickets, preferring one of more general connotation, namely, the Fanconi syndrome.

It is the purpose of the present communication to report on the results of the investigation of a typical case of the Fanconi syndrome and to submit an analysis of the relevant literature.

REPORT OF CASE

The patient, a white boy, was born on Nov. 26, 1929. The father's great-grandmother and the mother's grandmother were sisters, the first and last members of a large progeny; the boy's parents were second cousins once removed. The father was 49 and the mother 35 years old when the child was born. There had been no other pregnancies. Both parents were healthy. Aside from a report of "a tendency toward diabetes" on the paternal side, no history of heritable disease was elicited.

Birth occurred normally at term, the infant weighing 6 pounds 7 ounces (2.9 Kg.). Breast feeding was tried for only two months. Thenceforth an adequate diet was provided, which included customary supplements of vitamins A, C and D. The feedings were not well taken, and the gain in weight was not satisfactory; however, no especial concern was felt for the child's health during the first three years. Dentition began at 6 months; the boy started to walk at 13 months and to talk when he was about 18 months old. Growth in length was regarded as normal. At the age 3 years the child was considerably underweight. By 4 years he was thought to be seriously undernourished, and it was noted that he was knock kneed, that "his joints had become stiff" and that he walked with difficulty. Roentgen examination led to a recommendation that more cod liver oil be given. By 5 years the boy was unable to walk. During the ensuing three years he led a restricted life. A well designed and ample diet was offered but it was taken poorly. Cod liver oil and vitamin D concentrates were administered inconsistently. At the age of 8 years 7 months, a minor injury was followed by swelling of the left thigh. This episode occasioned admission to the hospital.

Although bedridden, apprehensive and irritable, the boy did not appear acutely ill. His color was good, containing no trace of the yellowish pallor that often marks prolonged failure of renal or hepatic function. His intellectual development was excellent. There was no acceleration of the respiratory rate. The temperature was 100.4 F. (38 C.), the pulse rate 100 beats per minute, and the systolic blood pressure 116 mm. of mercury and the diastolic 88. With the exception of the fact that the skull was normal in size, conformation and consistency, the child presented the classic deformities of rachitic dwarfism of severe degree (fig. 1). The total length was about 40 inches (99 cm.), approximately 20 per cent below the median value, of 50 inches (125 cm.), for healthy boys of 8 years. There was pronounced enlargement of the wrists, knees and ankles; a rickety rosary, Harrison's groove and pigeon breast were present together with conspicuous anteriorly convex bowing of both femurs and laterally convex curvature of the proximal portions of both humeri. Free motion between the proximal third and the distal two thirds of the left femur attested the presence of an ununited fracture. The spine showed little curvature; the fingers were normal.

The child was seriously undernourished. Subcutaneous fat was deficient in amount, and the voluntary musculature was wasted. The weight was 26 pounds (12 Kg.), about 27 per cent less than would be predicted from his total length and approximately 62 per cent under the median value for healthy boys of the same age.

The optic fundi showed no abnormalities. The state of dentition is illustrated in the following diagram. The Roman numerals designate deciduous and the Arabic permanent teeth; parentheses indicate that the tooth was in the process of eruption.

6, 0, IV, III, II, (1)	(1), II, III, IV, V, 0	Upper
0, V, IV, III, II, 1	1, II, III, IV, 0, 6	Lower
Right	Left	

The teeth were in good condition. The erupted members of the permanent denture failed to show the enamel hypoplasia to be expected had rickets been active and severe during the first year or two of life. The isthmus of the thyroid gland was normal; neither the lateral lobes nor nodules interpretable as enlarged parathyroid bodies could be felt. The heart and lungs presented no abnormalities. The wall of the abdomen was thin, but the liver, spleen and kidneys could not be felt. There were no noteworthy neurologic abnormalities.

Fig. 1.—The patient in June 1938, aged 8 years 7 months. The boy could sit erect only with difficulty and could not stand. There is conspicuous expansion of the wrists, knees and ankles. Anterior bowing of the femurs is evident, lateral curvature of the proximal portion of the humeri somewhat less clear. The thoracic deformities are not well shown. The head appears normal.

The concentration of hemoglobin was 16 Gm. per hundred cubic centimeters; the red blood cells numbered 5,000,000 and the leukocytes 7,000 per cubic millimeter. A stained smear showed 60 per cent of polymorphonuclear neutrophil cells, 1 per cent eosinophils and 39 per cent of lymphocytes.

The urine was cloudy, gave an acid reaction to litmus and had an uncorrected specific gravity of 1.022. Albumin was present in an amount designated 1 plus; a reducing substance of 4 plus concentration was also present. There was a small amount of acetone but no diacetic acid. A few granular and hyaline casts and cylindroids were noted. No leukocytes or epithelial cells were present. The concentration of organic acids was greatly increased.

The results of chemical examination of the blood are summarized in table 1.

Roentgenographic examination of the entire skeleton revealed atrophic rickets of extreme degree; numerous fractures were present. Attention is drawn to the specific features of the skeletal lesion in the legends of figures 2, 3, and 4.

The Mantoux test with 0.01 mg. of old tuberculin supplied by the New York City Board of Health elicited a negative reaction. A Kahn test of the blood serum like-

TABLE 1.—*Results of Chemical Examinations of the Blood.*

Date	Whole Blood, Mg. per 100 Cc.				Serum															
					Mg. per 100 Cc.				M. Eq. per Liter				Gm. per 100 Cc.				Mg. per 100 Cc.			
	Nonprotein Nitrogen	Urea	Urea/NPN	Sugar	Calcium	Phosphorus	Phosphatase Activity, Bodansky Units	Carbon Dioxide-Combining Power, per Cent	Bicarbonate	Chlorine	Sodium	Equivalent Vapor Pressure, Gm. Equivalents NaCl per 100 Gm. Water	Total Protein	Albumin	Globulin	Albumin/Globulin	Total Cholesterol	Ester Cholesterol	Free Cholesterol	Ester/Free
6/24/38	33.6	14.7	43.7	..	10.6	2.4	41.0	....	....	.....	.....	.....	....	....	....	...	.....	.....	....	...
6/26/38	....	....	....	..	....	...	42.0	....	....	.....	.....	.....	....	....	....	...	.....	.....	....	...
6/30/38	....	....	....	78	....	...	....	32.0	....	108.5	.....	.....	....	....	....	...	.....	.....	....	...
7/19/38	31.9	....	....	..	10.5	2.1	....	....	18.7	103.9	133.8	0.843	6.55	4.64	1.91	2.4	.....	.....	....	...
8/18/38	....	....	....	61	....	...	....	....	....	.....	.....	.....	....	....	....	...	.....	.....	....	...
11/ 2/38	33.6	....	....	63	10.3	1.8	....	32.0	....	.....	.....	.....	6.39	4.21	2.18	1.9	195.6	139.7	55.9	2.5
11/ 7/38	....	....	....	..	....	...	....	28.2	....	.....	.....	.....	....	....	....	...	.....	.....	....	...
11/11/38	....	....	....	..	....	...	....	29.8	....	.....	.....	.....	....	....	....	...	.....	.....	....	...
11/12/38	Serum 26.6	....	....	..	10.1	1.2	45.7	....	14.8	108.1	.....	.....	6.5	4.1	2.4	1.7	.....	.....	....	...
1/ 9/39	....	....	....	..	....	...	....	....	10.9	106.2	.....	.....	....	....	....	...	.....	.....	....	...

wise gave a negative result. The bleeding time was three minutes, and the clotting time by the capillary tube technic was one-half minute. Electrocardiographic examination revealed normal conditions.

A determination of the basal metabolic rate with the Benedict-Roth apparatus yielded a value for oxygen consumption of 111 cc. per minute. Calculations based on an assumed respiratory quotient of 0.82 resulted in a value for heat production of 32.15 calories per hour. With use of Boothby and Sandiford's modification of the Dubois standards for basal metabolic rate based on surface area, the child's

Fig. 2.—June 1938. Although the bones of the skull appear thin, lack of mineral is much less conspicuous here than in the rest of the skeleton. The teeth are well calcified. The sella turcica appears small.

rate was computed to be — 1.9 per cent. Calculations based on Talbot's standards,[19] with body weight used in the denominator, yielded a value of 7 per cent above normal. Inasmuch as the total length could not be measured accurately because of the boy's deformities, the latter figure is more significant.

19. Talbot, F. B.; Wilson, E. B., and Worcester, J.: Standards of Basal Metabolism of Girls (New Data) and Their Use in Clinical Practice, J. Pediat. **7**:655 (Nov.) 1935.

The child remained in the hospital for two months and was twice readmitted within the next six months. During these periods studies were carried out that will be referred to later. Attempts were made to institute treatment with dicalcium phosphate, vitamin D concentrates and a diet containing a moderate excess of mineral cationogens. Although the patient took approximately 5,000 U. S. P. units of vitamin D daily for several weeks, the program of treatment was frustrated by his capricious appetite and the parents' understandable reluctance to enforced dietary restrictions when the likelihood of recovery appeared so small.

The subsequent history is one of progressive failure of skeletal and muscular function. Death occurred in the course of an infection of the respiratory tract on Dec. 20, 1939, when the boy was 10 years 1 month of age. Necropsy was not performed.

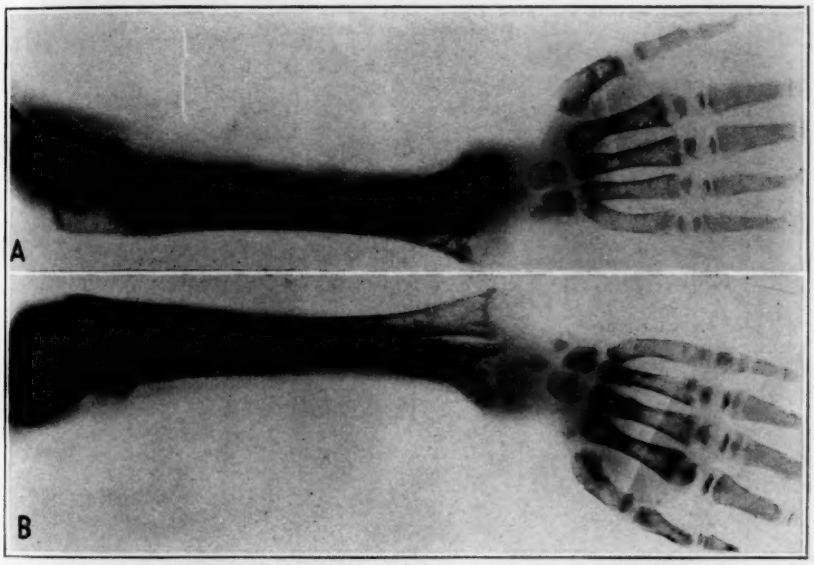

Fig. 3.—November 1938. *A*, the right forearm and hand. There is extreme atrophy of the cortex and spongiosa. No zone of preparatory calcification is visible. The distal ends of the radius and ulna show a fringed border that is pathognomonic of rickets. The rachitic intermediary zone is not so wide as it would be had not the plastic juxtaepiphysial plate of cartilage been compressed in the long axis and caused to protrude laterally. Near the distal end of the radius is a fracture with slight angulation; the presence of poorly mineralized callus demonstrates an attempt at repair. There is also a greenstick fracture through the proximal third of the ulna. *B*, the left forearm and hand. A greenstick fracture is present in the proximal third of the ulna; another fracture with angulation, through what appears to be an *Umbauzone* (zone of reconstruction), is seen in the distal third of the radius. There is an infraction of the cortex on the medial aspect of the first metacarpal bone. Only five poorly calcified centers of ossification can be recognized in the carpus; present are the capitate, hamate, triquetrum, lunate and greater multangular bones. The center for the distal end of the ulna has not appeared. According to Todd's standards this state of development is normal at 4 years. The patient was 9 years old.

METABOLIC OBSERVATIONS

Glycosuria.—The reducing substance was found to be entirely fermentable by yeast; this excluded the possibility that it was lactose, galactose or one of the pentoses and suggested that it was dextrose. More precise identification was not undertaken.

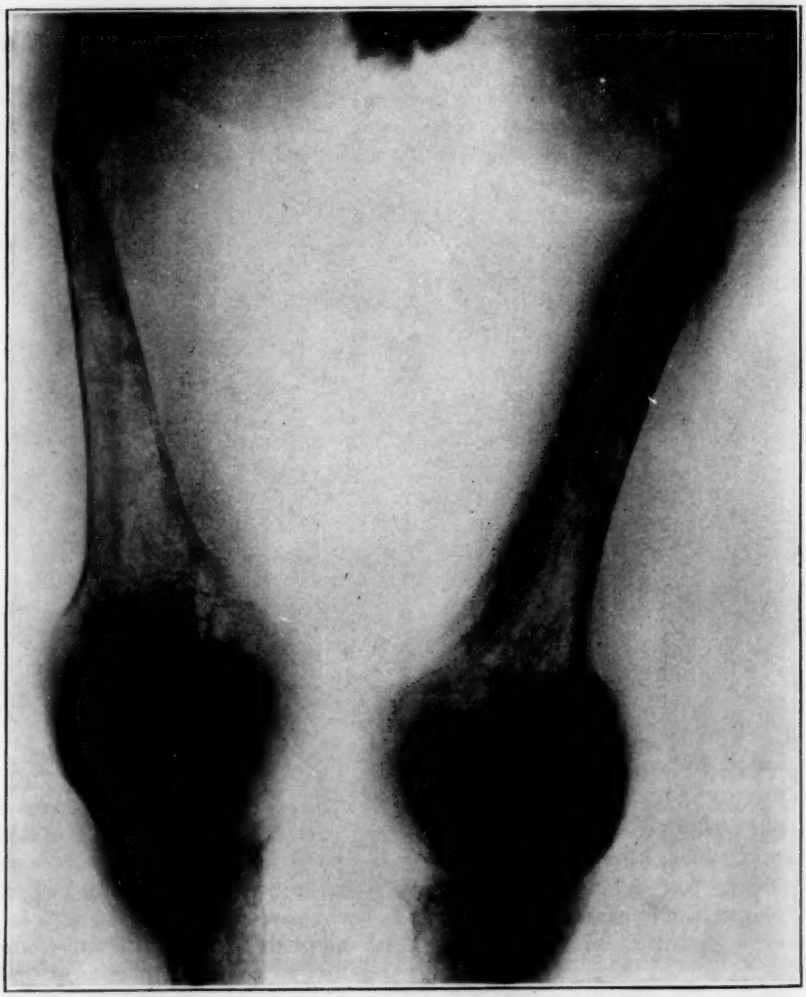

Fig. 4.—June 1938. The lower extremities show the same degree of rickets and osteoporosis as does the remainder of the skeleton. The fractures of the femurs never united.

Glycosuria was continuous. The mean daily excretion of sugar amounted to 18 Gm., with extremes of 37 and 12 Gm. The concentration in twenty-four hour specimens of urine averaged approximately 2 per cent, varying from 1 to 3 per cent. Acetone was usually present (from a trace to 1 plus); diacetic acid was frequently demonstrated in low concentration.

A study of the diurnal fluctuations in the excretion of sugar and their relation to the level of the blood sugar demonstrated that the glycosuria was of the renal type (fig. 5).

Fasting Blood Sugar.—The nondiabetic character of the glycosuria was confirmed by three determinations of the fasting blood sugar, which yielded values of 78, 61 and 63 mg. per hundred cubic centimeters respectively.

Dextrose Tolerance.—Two observations were made on the response of the blood sugar to the oral ingestion of 1.75 Gm. of dextrose per kilogram of body weight. The two tests gave similar values. One curve is reproduced in figure 5.

Epinephrine Test.—The subcutaneous injection of 0.3 mg. of epinephrine hydrochloride about three hours after breakfast promptly produced hyperglycemia of moderate degree; the time required for return of the blood sugar to normal was somewhat prolonged.

Renal Function.—In view of the normal values of the blood nonprotein nitrogen and the normal relation between nonprotein nitrogen and urea, further studies of

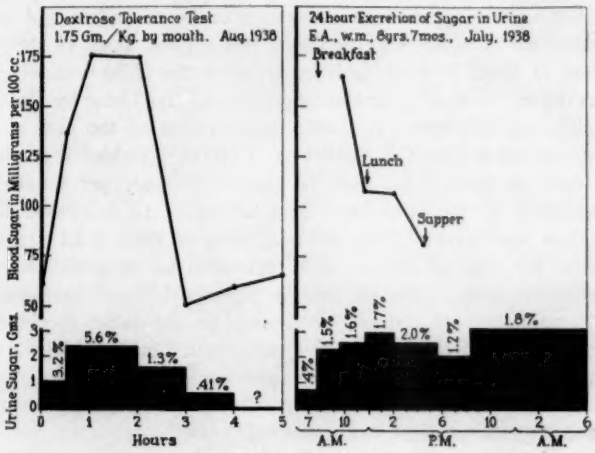

Fig. 5.—The relation between the blood sugar and urinary sugar. The concentration of urinary reductant is shown at the top of the columns.

the excretory capacity of the kidneys with reference to nitrogenous metabolites were not made.

Polyuria.—The twenty-four hour volume of urine remained consistently high. During a period of thirty-two days, embracing the hottest portions of July and August, the mean twenty-four intake of fluid was 1,092 cc.; the average volume of urine amounted to 836 cc., equivalent to 87 per cent of the fluid intake. During a period of nine days in November the intake averaged 1,079 cc. and the volume of urine 708 cc. daily; this represented 66 per cent of the intake of liquids.

Specific Gravity.—The specific gravity of the urine, not corrected for the effect of dextrose and of protein, remained in the neighborhood of 1.020. Restriction of fluid caused the specific gravity to rise to 1.035. One value of 1.010 was obtained under undefined circumstances.

Albumin.—Albumin was detected in every specimen that was examined. The concentration approximated 0.02 to 0.04 per cent. Quantitative determination of the protein was not made. Results of tests for Bence Jones proteose were negative.

Formed Elements.—Repeated examinations of the urinary sediment usually, but not invariably, revealed hyaline and granular casts. Numerous round cells, some bearing the appearance of leukocytes and others that of altered renal tubular epithelium, were usually observed. Occasionally there were a few erythrocytes, but chemical tests for hemoglobin when applied to the urine directly and to the sediment obtained by centrifugation invariably gave negative results.

Anion-Cation Equilibrium.—The observations on the anion-cation equilibrium, although numerous, are fragmentary.

Blood.—The presence of acidosis was indicated by the low values for carbon dioxide–combining power and bicarbonate concentration in the serum. Neither carbon dioxide tension nor p_H was measured.

In specimens of serum from blood that had not been protected against loss of carbon dioxide the chloride content showed moderate elevation, at one time reaching 108.5 milliequivalents per liter; in the only specimen manipulated under a seal of liquid petrolatum the concentration was 103.9 milliequivalents. The inorganic phosphorus content of the serum was reduced to less than 1 milliequivalent per liter; the protein content was normal. The concentrations of sulfate and organic acids were not measured. Preparations to titrate the organic acids of the blood serum by the method of Brühl [20] were under way when the child was withdrawn from medical supervision. The only determination of total fixed base by Hald's method [21] was technically unsatisfactory. A single measurement of the rate of evaporation of the serum, carried out by Dr. Robert W. Culbert,[22] yielded a normal value for equivalent vapor pressure, 0.843 Gm. of sodium chloride per hundred grams of water. Calculation of the total fixed base according to a method developed by Culbert, McCune and Weech [23] resulted in a value of 150.8 ± 2.1 (probable error) milliequivalents per liter of serum; this represents an approximately 3 per cent reduction below the mean value for healthy persons, 155 milliequivalents per liter. The only determination of sodium, performed on the same specimen of serum, yielded a concentration of 133.8 milliequivalents, about 8 milliequivalents (6 per cent) below the average normal figure. This approximates the degree of reduction of bicarbonate, which amounted to between 10 and 16 milliequivalents per liter. Potassium and magnesium were not measured.

Acidity of the Urine.—Specimens of fresh urine were invariably acid. The mean of 22 determinations of p_H made with the glass electrode was 5.70; the highest value was 6.8 and the lowest 4.79. These values were obtained with specimens that were collected without precautions to prevent loss of carbon dioxide. In view of the acid reaction of the urine, the omission of this precaution does not affect the interpretation of the resutls.

Ammonia.—The urinary concentration of ammonia was high. Five determinations of the ratio ammonia nitrogen: total nonprotein nitrogen in twenty-four hour specimens gave values of 0.09, 0.14, 0.19, 0.22 and 0.24, respectively. The average normal figure lies between 0.02 and 0.06.

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20. Brühl, H.: Eine Mikromethode zur direkten Bestimmung der organischen Säuren im Blutserum, Biochem. Ztschr. **256**:293, 1932.

21. Hald, P. M.: The Determination of the Bases of Serum and Whole Blood, J. Biol. Chem. **103**:471 (Dec.) 1933; A Note on the Gravimetric Determination of Total Base of Serum and Blood: A Correction, ibid. **105**:675 (July) 1934.

22. Culbert, R. W.: The Vapor Pressure of Human Blood by Hill's Thermoelectric Method: Apparatus and Technique, J. Biol. Chem. **109**:547 (May) 1935.

23. Culbert, R. W.; McCune, D. J., and Weech, A. A.: Rate of Evaporation in Serum as a Measure of Vapor Pressure, Osmotic Pressure, and Concentration of Solutes, J. Biol. Chem. **119**:589 (July) 1937.

Titrable Acid.—There was pronounced increase in the titrable acid, values of from 15 to 30 milliequivalents per twenty-four hours being obtained on several occasions. In view of the high concentration of organic acids, not all of this increase can be attributed to acid phosphate.

Mineral Balance.—A balance study of the metabolism of calcium, phosphorus, magnesium, sodium and chlorine was carried out in August 1938.

Standard collection procedures were employed in the study. The diet, urine, stools, refused food and water used in washing the dishes were prepared for analysis for calcium, phosphorus and magnesium by dry ashing in the presence of an excess of powdered sodium carbonate in pyrex vessels at 400 C. Silicon was removed

TABLE 2.—*Data from Studies of Mineral Metabolism* *

Per Day	Calcium, Gm.	Phosphorus, Gm.	Magnesium, Gm.	Sodium, Gm.	Chlorine, Gm.
Period 1, Three Days					
Intake	0.830	0.877	0.137		
Output:					
Urine	0.117 (20%)	0.518 (61%)	0.047 (33%)		
Stool	0.457 (80%)	0.336 (39%)	0.097 (67%)		
Total	0.574	0.854	0.144		
Balance	+0.256	+0.023	−0.007		
Balance/d/k	+0.021	+0.0019	−0.0006		
Balance/intake × 100	+31%	+2.6%	−5.1%		
Net absorption	0.373	0.541	0.040		
Urine/net absorption × 100	31%	96%	118%		
Period 2, Six Days					
Intake	0.745	0.473	0.120	0.599	1.023
Output:					
Urine	0.065 (10%)	0.458 (62%)	0.036 (33%)	0.586 (97%)	1.083 (96%)
Stool	0.613 (90%)	0.286 (38%)	0.073 (67%)	0.016 (3%)	0.045 (4%)
Total	0.678	0.744	0.009	0.602	1.128
Balance	+0.067	−0.271	+0.011	−0.003	−0.105
Balance/d/k	+0.0055	−0.022	+0.0008	−0.0002	−0.0085
Balance/intake × 100	+9%	−57%	+9%	−1%	−10%
Net absorption	0.132	0.187	0.047	0.583	0.978
Urine/net absorption × 100	49%	245%	77%	100%	111%

* This study was made during August 1938, when the boy was 8 years 8 months old. His mean weight during the period of study was 12.3 Kg. The diet was of general composition and produced approximately neutral ash. It supplied a total of 1,265 calories per day, distributed as follows: protein 14 per cent, carbohydrate 43 per cent and fat 43 per cent.

by repeated evaporation to dryness of the dissolved ash with strong hydrochloric acid, followed by dilution and filtration. Material for analysis for sodium and chloride was prepared by prolonged digestion of the dried material with concentrated nitric acid saturated with silver nitrate. Values for calcuim, phosphorus and magnesium were determined gravimetrically by the method of Washburn and Shear [24]; for sodium, by the gravimetric method of Butler and Tuthill [25]; for chlorine, by weighing silver chloride.

The child disliked the experimental diet and refused food consistently. In view of what will be said later it is of interest that he manifested a lively desire for meat.

24. Washburn, M. L., and Shear, M. J.: Composition of Bone: XIII. Direct Gravimetric Determination of Ca, Mg, and PO_4, J. Biol. Chem. **99**:21 (Dec.) 1932.

25. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J. Biol. Chem. **93**:171 (Sept.) 1931.

The details of the balance study are summarized in table 2. During the first period, when the intake of calcium and phosphorus was adequate, the child was in positive balance with respect to both minerals; the retention of calcium can be termed average, while the retention of phosphorus was extremely small. An insignificant loss of magnesium occurred. During the second period, when refusal of food curtailed the intake of mineral, the calcium balance was reduced but still not below the range of normal variation; the balance of phosphorus became negative. The virtually unaltered character of the magnesium balance is regarded as a check on the completeness of collection of specimens. During this period the child excreted slightly more sodium and chlorine than he ingested.

It is worth while to point out that during the first period, when the intake of calcium was ample as judged by normal requirements, the net absorption [26] of calcium amounted to 45 per cent of the intake and hypercalciuria existed; both tended to diminish as the amount of dietary calcium was reduced but never reached the low level that would be anticipated in rickets of comparable severity due to

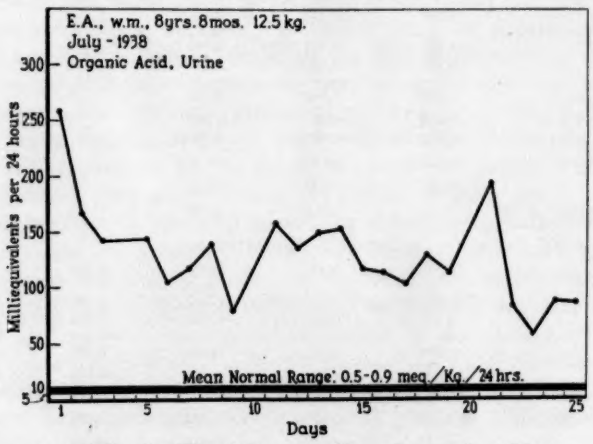

Fig. 6.—The daily excretion of organic acids.

vitamin deficiency. In relation to the total excretion of phosphorus the urinary content of phosphorus was high in both periods. In the second period there was eliminated in the urine alone 62 per cent of the total excretion of phosphorus, 97 per cent of the phosphorus contained in the diet and 240 per cent of the net absorbed amount. The distribution of magnesium, sodium and chlorine between the urine and the stools conformed to normal relations.

Organic Acids.—As determined by the technic of Van Slyke and Palmer [27] the concentration of organic acids and the amount excreted in twenty-four hours were found to be greatly increased (fig. 6). Whereas the healthy growing person excretes approximately 1 milliequivalent per kilogram of body weight per day,[28]

26. Harris, L. J.: The Mode of Action of Vitamin D: The "Parathyroid" Theory; Clinical Hypervitaminosis, Lancet **1**:1031, 1932.

27. Van Slyke, D. D., and Palmer, W. W.: Studies of Acidosis: XVI. The Titration of Organic Acids in Urine, J. Biol. Chem. **41**:567 (April) 1920.

28. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 469.

the patient's urine contained on the average 10 milliequivalents per kilogram per day. Wide fluctuations were observed; the smallest amount excreted in a single twenty-four hour period was 4 and the largest 20 milliequivalents per kilogram.

Acting on Fanconi's conjecture [13c] that the organic acids might be of the amino acid series, a fractional analysis of the urinary nonprotein nitrogen was made. The results are summarized in table 3. The large size of the undetermined nitrogen fraction supported Fanconi's suspicion that at least part of the organic acids were amino in character.

Pending the results of chemical identification of the acids, an attempt was made to obtain further indirect evidence of their nature and to acquire information of possible therapeutic value by dietary experiments. On successive days the daily consumption of protein was alternately increased by feeding cottage cheese and decreased by starvation or by allowing no food but levulose. The experimental period lasted ten days. The twenty-four hour collection of urine for each day was divided into several portions with relation to meals; the separate specimens were analyzed quantitatively for their content of organic acid and sugar and qualitatively for ketones.

TABLE 3.—*Fractions of Urinary Nonprotein Nitrogen* *

Constituent	Normal Value,[28] per Cent of Total Nonprotein Nitrogen	Patient's Urine, per Cent of Total Nonprotein Nitrogen
Ammonia	4	23.6
Urea	83	38.9
Uric acid	1	2.4
Creatine	6	1.1
Creatinine	..	2.0
Undetermined nitrogen (amino acids, etc.)	6	32.0
Total nonprotein nitrogen	100	100.0

* Specimen of urine collected between 6 a. m. and 12 noon, Nov. 2, 1938. The patient was receiving a diet of average composition, of which he partook poorly.

Although the rate of excretion of organic acids was highly variable during the intervals when the patient ate a general diet, there was conspicuous decrease in the amount of organic acid and of sugar in the urine on a single day when almost nothing but levulose was given until late in the afternoon. This fact was interpreted to suggest that some of the acids were of the amino acid series and also that the patient's ability to metabolize levulose was not reduced.

Chemical Identification of Organic Acids.—In June 1939, while the child remained at home partaking of a general diet and receiving no medication, the urine voided during a period of six days was collected. The volume of the specimen was 3,810 cc. The concentration of albumin was 2 plus. A test with Sulkowitch's [29] reagent indicated more than 10 mg. of calcium per hundred cubic centimeters; a trace of acetone was present but no diacetic acid. Microscopic examination revealed many finely granular casts and cylindroids. Cellular elements were not noted.

Of this sample 3,600 cc., containing 360 milliequivalents of organic acid, was rendered alkaline with calcium hydroxide and filtered to remove the inorganic phosphorus. The filtrate was acidified to congo red (p_H 5.5) with sulfuric acid

29. Barney, J. D., and Sulkowitch, H. W.: Progress in the Management of Urinary Calculi, J. Urol. **37**:746 (June) 1937.

and refiltered with the aid of decolorizing charcoal to remove traces of water-insoluble acids. It was then neutralized with an excess of calcium carbonate, filtered a third time and concentrated [30] under reduced pressure at 30 to 40 C. to 250 cc. The resulting heavy syrup was again acidified with sulfuric acid, but an attempt to extract the ether-soluble constituents in a continuous extractor failed, owing to the formation of a gelatinous emulsion. The acid mixture was therefore treated with five successive 400 cc. portions of acetone; this dissolved the urea and organic acids other than amino acids and precipitated the latter. The acetone-insoluble fraction was found to contain 289 milliequivalents of organic acid and a comparable amount of amino nitrogen. An aliquot portion was accordingly treated by the procedure of Neuberg and Kerb [31] for the separation of amino acids. The resulting fraction showed the presence of 273 milliequivalents of organic acids and 282 milliequivalents of amino nitrogen; the latter fraction was increased to 316 milliequivalents by acid hydrolysis. These results indicate that the organic acids in this fraction consisted mainly of amino acids together with some peptides.

The filtrate from the acetone-insoluble fraction was neutralized with a suspension of calcium carbonate in water and freed of acetone by distillation. The residue was rendered strongly acid with 15 cc. of ten times normal sulfuric acid and extracted with ether in a continuous extractor for forty-eight hours. The residual solution of ether-insoluble substance contained 92 milliequivalents of organic acids. Treatment by the procedure of Neuberg and Kerb yielded a fraction containing 42 milliequivalents of organic acid and 56 milliequivalents of amino nitrogen; these values were increased by acid hydrolysis to 50 and 104 milliequivalents, respectively, which demonstrated that the fraction consisted largely of amino acids and peptides. No attempt was made to recover the missing 50 milliequivalents of organic acid not precipitated by the Neuberg and Kerb procedure.

The ethereal extract was diluted with water and freed of the ether on the steam bath. The residual aqueous solution of about 100 cc. was faintly cloudy owing to the presence of water-insoluble oils; these were removed by shaking with 80 cc. of purified petroleum benzine (petroleum ether). The clear aqueous solution, which was found to contain 78 milliequivalents of organic acid, was made up to 250 cc. This solution proved to be levorotatory, —0.73° (2 dcm.); from this value the presence of both lactic and betahydroxybutyric acids was suspected. Analysis by the method of Mondschein [32] indicated the presence of 41 milliequivalents of lactic acid and 29 milliequivalents of betahydroxybutyric acid.

The 360 milliequivalents of organic acid found in the original specimen was therefore somewhat more than accounted for by the following values:

	Milliequivalents	Composition, Per Cent	Amount Excreted per 24 Hours Milliequivalents
Amino acids and peptides.....	315	82	52.5
Lactic acid	41	11	6.8
Betahydroxybutyric acid	29	7	4.8
Total	385	100	64.1

30. In a preliminary experiment with another sample of the patient's urine crystals of tyrosine separated at this stage of the procedure.

31. Neuberg, C., and Kerb, J.: Ueber ein Fällungsmittel für Aminosäuren, Biochem. Ztschr. **40**:498, 1912.

32. Mondschein, J.: Quantitative Bestimmung der Milchsäure neben β-Oxybuttersäure, Biochem. Ztschr. **42**:91, 1912.

The amino acid mixture contained besides tyrosine about 16 per cent of monoaminodicarboxylic acids. Positive reactions were obtained for cystine and other amino acids commonly found in proteins. At no stage of the procedure was a disproportionate amount of any single acid, including cystine, encountered.

In another sample of urine from the same patient and in a composite sample of urine obtained from healthy medical students the acetone-insoluble fractions likewise proved to consist of mixtures of amino acids and peptides:

	Milliequivalents per Liter	
	Organic Acid	Amino Nitrogen
Patient's urine (65 milliequivalents of organic acids per liter):		
Acetone-insoluble fractions before hydrolysis.....	42	42
Acetone-insoluble fractions after hydrolysis.....	57	52
Normal urine (29 milliequivalents of organic acids per liter):		
Acetone-insoluble fractions before hydrolysis.....	2.1	1.2
Acetone-insoluble fractions after hydrolysis.....	2.7	2.2

Résumé.—The patient, a boy, was recognized to have rickets when he was 3 years old; the disorder was doubtless present somewhat earlier, although the excellent state of the enamel of the permanent teeth argued against the existence of severe defect of calcification during infancy. At no time was specific treatment employed in amount sufficient to justify the assertion that the disease could not be controlled by vitamin D. However, the absence of healing after three months' treatment with 5,000 U. S. P. units of vitamin D daily warrants the conclusion that the process was, if not intractable, at least resistant. When the boy was 9 years old, dwarfism, undernutrition and atrophic rickets were present. The urine consistently contained albumin, sugar and casts together with a large excess of organic acids. Of these, 82 per cent was amino acids of mixed type, 11 per cent lactic acid and 7 per cent betahydroxybutyric acid. The urine was acid and contained much ammonia; the twenty-four hour volume was increased. The significant biochemical changes in the blood were pronounced reduction of bicarbonate and extreme lowering of the serum inorganic phosphorus level; calcium, nonprotein nitrogen and urea were within normal limits. The concentration of organic acids was not determined. The total fixed base and sodium were slightly diminished. A metabolism study demonstrated excessive renal excretion of phosphorus. The balance for this ionogen became negative when the intake was reduced to levels at which a healthy person would be expected to conserve phosphorus by restricting its elimination through the kidneys.

Interpretation.—The glycosuria in this case was of the renal type; hence, it is warranted to conclude that it was due to functional incapacity of the renal tubular epithelium to resorb dextrose at the rate maintained by glomerular filtration. Since there is general agreement concerning the site of resorption of dextrose,[33] it is possible to assign the defect to the proximal convoluted tubule.

We are disposed to stress the observation that the nonprotein nitrogen and urea of the blood were not increased. This permits the

33. Richards, A. N.: The Croonian Lecture: Processes of Urine Formation, Proc. Roy. Soc., London, s.B **126**:398 (Dec.) 1938.

deduction that significant hyperaminoacidemia was not present. Hence, it can be inferred that the high urinary content of amino acids was due to defect of tubular resorption and not to increased concentration of amino acids in the glomerular filtrate. It is not possible to specify the part of the tubular system in which amino acids are resorbed.[34] Accordingly, we cannot assert that tubular incompetence with relation to the resorption of dextrose implies similar insufficiency with regard to amino acids.

Explanation of the daily excretion of approximately 5 milliequivalents of betahydroxybutyric acid presents no difficulty, even without postulating defect of resorption. That intense renal glycosuria can produce ketosis has been demonstrated by clinical [35] and experimental observations. The phenomenon is related either to diminution of glycogen reserves brought about through incessant waste of dextrose by the kidneys or, according to Somogyi's [36] interpretation, to acceleration of the rate of hepatic glycogenolysis under the stimulus of a rapid fall of the blood sugar level.

Our data do not suffice to make clear the reason for the presence of 11 per cent of lactic acid in the urinary organic acid mixture. Failure to determine the blood organic acids is particularly embarrassing at this point. It is obvious that if the level of lactic acid were known to be normal the increased urinary excretion could be explained only by decreased resorption, whereas an elevated concentration in the blood would point to extrarenal disturbance of function, presumably in the liver or muscles.

With regard to the moderate degree of polyuria presented by this patient, it appears reasonable to assume that it was caused in part by the maintenance of high osmotic pressure in the glomerular filtrate due to the nonresorption of dextrose and in part by the acidosis; the possibility of tubular incompetence in relation to the conservation of water also merits attention.

The presence of rickets and atrophy of bone finds simplest explanation in the extremely low concentration of inorganic phosphorus in the serum. The balance study demonstrated that hypophosphatemia was due to loss of phosphorus in the urine. Hyperphosphaturia may have been caused by acidosis. Also it is justifiable to suspect that some degree of compensatory hyperparathyroidism may have been present. Finally, it is conceivable—and this is the view which we most favor—that the phenomenon may have resulted from a defect of the phosphate-

34. Richards, A. N.: Personal communication to the authors.

35. Babson, S. G.: Renal Glycosuria: A Hereditary and Clinical Study of One Family, J. Pediat. **17**:781 (Dec.) 1940.

36. Somogyi, M.: Changes in Ketonemia and Ketonuria During Hypoglycemia, Proc. Soc. Exper. Biol. & Med. **45**:644 (Nov.) 1940.

resorbing mechanism. This was assigned by Richards [33] to the proximal convoluted tubules and by Smith [37] to the distal. Inasmuch as the resorption of dextrose is mediated through the formation of phosphate esters, such an assumption supplies a speculative nexus between the glycosuria and the hyperphosphaturia.

The foregoing explanation ascribes to defective function of those portions of the renal tubular system which are concerned with the resorption of dextrose, phosphorus and amino acids the principal role in the production of the symptom complex manifested by the patient. The hypothesis rests on several assumptions. Among these that of normal hepatic function is an important one. Lacking observations on this subject, we turn to the literature for information.

REVIEW OF THE LITERATURE RELATING TO THE FANCONI SYNDROME AND CLINICALLY SIMILAR DISORDERS

(The appendix contains abstracts of these cases; summary data appear in table 4.)

General Description.—An attempt has been made to assemble the reports of or allusions to rickets accompanied by nondiabetic glycosuria which have appeared from time to time during the past fifteen years. We have found the following instances:

1. Fourteen cases [38] of hypophosphatemic rickets and glycosuria in young subjects in which the pathologic substrate is unknown or, for reasons which will be revealed presently, uncertain.

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37. Smith, H. W.: The Physiology of the Kidney, New York, Oxford University Press, 1937.

38. (*a*) Schier, A., and Stern, A.: Ueber einen Fall von unheilbarer Rachitis, Arch. f. Kinderh. **78**:176, 1926. (*b*) DeToni, G.: Remarks on the Relations Between Renal Rickets (Renal Dwarfism) and Renal Diabetes, Acta pædiat. **16**: 479, 1933. (*c*) Debré, R.; Marie, J.; Cléret, F., and Messimy, R.: Rachitisme tardif coexistent avec une néphrite chronique et une glycosurie, Arch. de méd. d. enf. **37**:597, 1934. (*d*) van Creveld, S.: Cirrhosis of the Liver and Hydronephrosis, Maandschr. v. kindergeneesk. **3**:504 (Sept.) 1934. (*e*) Guild, H. G.; Pierce, J. A., and Lilienthal, J. L.: An Unfamiliar Rachitic Syndrome, Am. J. Dis. Child. **54**: 1186 (Nov.) 1937. (*f*) Guild, H. G.: Personal communciation to the authors. (*g*) Pincus, J. B., in discussion on Guild, Pierce and Lilienthal.[38e] (*h*) Gittleman, I. F., and Pincus, J. B.: Rickets Associated with Dwarfism, Glycosuria, Ketonuria and Albuminuria, Am. J. Dis. Child. **60**:1351 (Dec.) 1940. (*i*) Smyth, F. S., in discussion on Guild, Pierce and Lilienthal.[38e] (*j*) Nobécourt, P.; Cathala, J.; Briskas, S. B., and Morel: Grand rachitisme hypotrophique et ostéomalacique avec hépatosplénomégalie, glycosurie, albuminurie, hypophosphatémie et acidose (Nanisme glyconéphrotique avec rachitisme hypophosphatémique de Fanconi), Arch. de méd. d. enf. **41**:204 (April) 1938. (*k*) Goldmann, F., and Ekstein, G.: Renal Dwarfism Due to Tubular Dysfunction: Clinical and Metabolic Studies of a Case, J. Pediat.

(Footnote continued on next page)

TABLE 4.—*Clinical Data Relating*

Case No.	Author and Reference	Year	Sex	Parental Consanguinity	Familial Incidence	Age: Onset	Age: Death	Rickets, Severity	Liver Enlarged	Blood Chemistry: Serum, Mg. per 100 Cc.: Ca	Blood Chemistry: Serum, Mg. per 100 Cc.: P	Blood Chemistry: Whole Blood Nonprotein N., Mg. per 100 Cc.	Blood Chemistry: Blood Sugar, Mg. per 100 Cc.: Fasting	Blood Chemistry: Blood Sugar, Mg. per 100 Cc.: Maximum	Blood Chemistry: Serum or Plasma CO_2 C. P. Vol. %
	1. Rickets; Glycosuria; Hypophosphatemia; Pathologic Anatomy Unknown or Uncertain														
1	Schier and Stern [38a]	1926	♂	—	—	2 mo.	18 mo.	++++	0	10.8-12.3	1.2-2.7	—	90-135	150	–
2	Boyd [1e]	1927	♂	—	—	Infancy	8 yr.	++++	—	8.2-11.4	1.5-5.9	36	48-103	250	22-49
3	Boyd [1e]	1927	♂	—	—	Infancy	2½ yr.	++++	—	8.5-9.2	1.3-2.0	53	—	120	52-61
4	De Toni [38b]	1933	♀	+	—	Infancy	Alive at 5 yr.	++++	—	9.8	2.5	43	80-88	197	22
5	Debré [38c]	1934	♀	—	—	4 yr.	11 yr.	++++	0	—	—	Urea N 36	91	200	–
6	Van Creveld [38d]	1934	♀	—	—	5 mo.	11 mo.	++++	+	9.9	1.2	23-26	52	141	–
7	Fanconi [13c] (case 2)	1936	♀	+	0	6 mo.	16 mo.	++	+ (soft)	9.6	2.2	35	68-161	340 Dextrose and epinephrine	–
8	Fanconi [13c] (case 3)	1936	♀	?	+	15 mo.	Alive at 2 yr.	++++	0	7.7-10.6	1.0-2.8	21-40	77-138	375 Dextrose and epinephrine	32
9	Guild et al. [38e,f]	1937	♀	0	—	6 mo.	22 mo.	++++	+ (hard)	±8	±1.3	±30	60	180	±30
10	Gittleman and Pincus [38g,h]	1937	♀	0	?	3½ yr.	Alive at 7½ yr.	++	0	9.2-11.5	1.5-3.3	16-34	50-100	225	28-54
11	Smyth [38i]	1937	♀	—	—	—	Alive at 5 yr.	—	—	—	1.5-5.0	—	—	—	Reduced
12	Nobécourt et al. [38j]	1938	♀	0	—	2 yr.	Alive at 4 yr.	++++	+ (hard)	8.8-9.7	1.5-1.8	38-42	73-150	170	28-55
13	Goldmann and Ekstein [38k]	1939	—	0	—	18 mo.	Alive at 2 yr.	++++	—	14.1-17.6	1.4-2.1	32	50-65	—	–
14	McCune et al.	1939	♂	+	0	2-3 yr.	10 yr.	++++	0	10.1-10.6	1.2-2.4	32-34	61-78	175	28-32
	1 a. Osteoporosis; Glycosuria; Hypophosphatemia; Pathologic Anatomy Unknown (Adults)														
15	Hunter	1935	♂	—	—	Adult life	Alive at 14 yr.	Osteoporosis, fractures	—	9.8-11.9	0.4-2.3	—	86	133	–
16	Hunter [39]	1935	♂	—	—	Childhood?	Alive at 29 yr.	Osteoporosis, fractures	—	9.5-11.6	1.0-2.8	Urea clearance ±50%	57	100	–
	2. Rickets; Glycosuria; Hypophosphatemia; Cystinosis														
17	Russell and Barrie (case 1) [41]	1936	♀	—	+	14 mo.	13 yr.	++++	?	10	3	Urea N 15	90	154	–
	3. Rickets; Glycosuria; Hyperphosphatemia; Pathologic Anatomy Inconclusive														
18	Danis and Rossen [42]	1941	♂	—	+ Brother of 19	Infancy	3 yr.	++++	—	8.1-9.1	4.9-6.7	32-60	96-143	222	–
19	Danis and Rossen [42]	1941	♀	—	+ Sister of 18	—	Alive at 9 yr.	+	—	6.9-9.7	3.2-6.1	30-70	82-95	286	–
	4. Rickets; Glycosuria (?); Hyperphosphatemia; Cystinosis														
20	Hottinger [43a]	1941	♂	0	+ Brother of 21	12 mo.	7½ yr.	++++	+ (hard)	11.5-5.1	7.0-9.5	29-129	64-135	—	–
21	Hottinger [43a]	1941	♀	0	+ Sister of 20	8 days	Alive	No rickets	—	—	—	—	—	—	–

Urine												Autopsy Findings			
					Blood Cells		Increased								
Specific Gravity	*pH*	Albumin	Sugar	Casts	White	Red	NH_3	PO_4	Ketone	Organic Acids	Cystine	Rickets	Kidneys	Liver	Cystinosis	Comments
1. Rickets; Glycosuria; Hypophosphatemia; Pathologic Anatomy Unknown or Uncertain																
—	5.3-7.0	—	2-4%	—	—	—	+	—	+	—	—	++++	Coagulum in tubules	Normal	—	
—	—	—	24-94 Gm. 24 hr.	—	—	—	—	—	+ ++++	—	—	..	.....	.....	..	No autopsy
—	—	—	2%	—	—	—	—	—	—	—	—	..	.....	.....	..	No autopsy
1.023-1.032	—	—	3-4%	+	+	0	—	—	Trace	—	—	..	.....	.....	..	Alive
1.031	Acid	0.2%	1.5% (?)	+	+	0	+	—	+	Incr.	—	..	.....	.....	..	No autopsy
High"	—	++	1.2%	—	+	—	—	—	+	—	—	—	Enlarged; glomerular epithelium cuboidal; tubules dilated; epithelium flat	Cirrhosis	—	Urine contained glycuronic acid
—	—	++	3.1-5.7%	++	++	?	—	—	+	—	—	—	Fatty infiltration of proximal tubules	Fragile; fatty infiltration	—	
1.005-1.020	6.7-7.3	0.6-7.0%	0.4-0.8%	+	+	+	+	+	+	Incr.	—	—	.....	.....	..	Alive
1.015 (corrected)	6.5	+	20-30 Gm. 24 hr.	+	+	—	+	+	+	Incr.	—	..	Swelling of tubular epithelium	Cirrhosis	—	
1.012-1.028	Acid	Tr.-+	Up to 0.4% dextrose and fructose	+	—	—	—	+	+	—	—	..	.....	.....	..	Alive
—	—	Tr.	+(?)	—	—	—	—	—	—	—	—	..	.....	.....	..	Alive
—	7.2-7.3	0.5-0.8%	Tr.-3 Gm. 24 hr.	—	+	0	—	?	+	—	—	..	.....	.....	..	Alive
1.003-1.035	Alk.	+	2%	+	0	0	—	0	+	Incr.	—	..	.....	.....	..	Alive
1.010-1.035	4.8-6.8	+	Up to 18 Gm. 24 hr.	+++	+	?	+	+	+	Incr.	0	..	.....	.....	..	No autopsy
1 a. Osteoporosis; Glycosuria; Hypophosphatemia; Pathologic Anatomy Unknown (Adults)																
—	—	—	+	—	—	—	—	—	—	—	—	..	.....	.....	..	Alive
—	Acid	+	+	0	+	—	—	—	—	—	—	..	.....	.....	..	Alive
2. Rickets; Glycosuria; Hypophosphatemia; Cystinosis																
—	—	+	+	+	—	+	—	—	—	—	—	++++	Glomerular reduction; tubular atrophy and hypertrophy; interstitial fibrosis	Focal necrosis	+	
3. Rickets; Glycosuria; Hyperphosphatemia; Pathologic Anatomy Inconclusive																
1.002-1.006	—	Tr.	++	+	+	+	—	—	+	—	—	+++	Glomerular sclerosis; tubular epithelium swollen and vacuolated	Normal	—	
1.004-1.006	—	Tr.	+	+	0	0	—	—	0	—	—	..	.....	.....	..	Alive
4. Rickets; Glycosuria (?); Hyperphosphatemia; Cystinosis																
1.008-1.015	—	Tr.-0.7%	+ 0	+	+	+	+	—	±	Incr.	0	..	Glomerular damage; atrophy and hypertrophy of tubular epithelium	Normal	+	Organic acids increased agonally
—	—	?	—	—	—	—	—	—	—	—	+	..	.....	.....	..	Alive

Case No.	Author and Reference	Year	Sex	Parental Consanguinity	Familial Incidence	Age: Onset	Age: Death	Rickets, Severity	Liver Enlarged	Blood Chemistry: Serum, Mg. per 100 Cc.: Ca	Blood Chemistry: Serum, Mg. per 100 Cc.: P	Blood Chemistry: Whole Blood Nonprotein N., Mg. per 100 Cc.	Blood Chemistry: Blood Sugar, Mg. per 100 Cc.: Fasting	Blood Chemistry: Blood Sugar, Mg. per 100 Cc.: Maximum	Serum or Plasma CO_2 C. P. Vol. %
	5. Rickets; Glycosuria; Serum Phosphate Unknown; Pathologic Anatomy Unknown														
22	Fairbank [44a]...	1926	♀	—	—	—	Girlhood	—	—	—	—	—	—	—	—
23	Fairbank [44a]...	1926	♀	—	—	—	12 yr.	++++	—	—	—	—	—	—	—
24	Hess et al.[44b]..	1930	—	—	—	—	—	—	—	—	—	—	—	—	—
25	Hess et al.[44b]..	1930	—	—	—	—	—	—	—	—	—	—	—	—	—
26	Hess et al.[44b]..	1930	—	—	—	—	—	—	—	—	—	—	—	—	—
27	Fanconi [13c,d].. (case 1)	1931	♀	0	—	3 mo.	5½ yr.	++++	—	—	—	40-83	56-160	—	—
28	Fornara [44c,d]..	1935	♂	—	—	15 mo.	Alive at 8 yr.	++	0	"4.852"	"5.842"	32-39	82-92	155	—
29	Caussade et al [44e]	1940	♂	—	—	15 mo.	Alive	++++	—	10.5	—	—	—	—	50
	6. Rickets; Glycosuria; Serum Phosphate Unknown; Cystinosis														
30	Lignac [45a].....	1924	♂	—	—	1 yr.	3 yr.	++++	0	—	—	—	—	156	—
31	Beumer and Weppler [45f]	1937	♂	—	—	9 mo.	10 mo.	++++	0	—	—	26-98	96-135	197	—
	7. Rickets; No Glycosuria; Hypophosphatemia; Cystinosis (?)														
32	Pache [46].....	1940	♀	+	+ Sister of 33	8 mo.	Alive at 5 yr.	++	—	9.4-11.8	2.8-4.1	26-42	48	—	—
33	Pache [46].....	1940	♂	+	+ Brother of 32	8 mo.	Alive at 2¼ yr.	++++	—	10.7-10.8	3.9-4.8	23	—	—	—
	8. Rickets; No Glycosuria; Serum Phosphate Unknown; Cystinosis														
34	Lignac [45d].....	1926	♂	—	?	Birth(?)	2 yr.	++++	—	—	—	—	—	—	—
35	Lignac [45e].....	1926	♀	—	—	Infancy	14 mo.	?	—	—	—	—	—	—	—
	9. Rickets; Glycosuria Unknown; Serum Phosphate Unknown; Cystinosis														
36	Benoit [48].....	1935	♂	—	—	—	3½ yr.	++++	—	—	—	—	—	—	—
	10. No Rickets; Glycosuria Unknown or No Glycosuria; Serum Phosphate Unknown; Cystinosis														
37	Abderhalden [49]	1908	♂	—	+	—	21 mo.	No rickets	—	—	—	—	—	—	—
38	Russell and Barrie [41] (case 2)	1936	♂	—	—	?	16 yr.	No rickets	—	Spinal fluid 4.6	—	Spinal fluid urea N ±120	—	—	—
39	Rössle [49c].....	1938	♀	—	—	—	4 yr.	No rickets	—	—	—	—	—	—	—

1a. Two cases [39] of osteoporosis with hypophosphatemia and glycosuria in adults, without autopsy.[40]

15:53 (July) 1939. (*l*) McCune, D. J.; Mason, H. H., and Clarke, H. T.: Late Rickets with Glycosuria and Organic Acid Acidosis (Fanconi Type), Am. J. Dis. Child. **58**:673 (Sept.) 1939. (*m*) Boyd (footnote 1 *a* and *b*). (*n*) Boyd and Stearns (footnote 1 *c* and *e*). (*o*) Fanconi (footnote 13 *b* and *c*). (*p*) Sturzenegger.[13d]

39. (*a*) Hunter, D.: Studies in Calcium and Phosphorus Metabolism in Generalized Diseases of Bones, Proc. Roy. Soc. Med. **28**:1619 (Oct.) 1935. (*b*) Fletcher, E.: ? Generalized Osteitis Fibrosa: A Case for Diagnosis, ibid. **28**:101 (Dec.) 1934.

(Footnotes continued on next page)

Urine												Autopsy Findings			
					Blood Cells		Increased								
Specific Gravity	p_H	Albumin	Sugar	Casts	White	Red	NH_3	PO_4	Ketone	Organic Acids	Cystine	Rickets	Kidneys	Liver	Cystinosis	Comments
				5. Rickets; Glycosuria; Serum Phosphate Unknown; Pathologic Anatomy Unknown												
–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	
–	–	–	+	–	–	–	–	–	–	–	–	–	Undescribed changes	–	–	
–	–	–	+	–	–	–	–	–	–	–	–	–	.....	..	..	No information
–	–	–	+	–	–	–	–	–	–	–	–	–	.....	..	..	No information
–	–	–	+	–	–	–	–	–	–	–	–	–	.....	..	..	No information
1.007	–	0.5-2.0%	0.5-2.5%	+	+	0	–	?	0	–	–	++++	Degeneration of tubular epithelium	–	?	Cystinosis suspected
1.014-1.025	–	0.025-0.05%	0.6-2.0%	+	+	–	–	–	–	–	–	..	.....	.....	..	Alive
–	–	Tr.	Tr.	+	+	+	–	+	0	–	–	..	.....	.....	..	Alive
				6. Rickets; Glycosuria; Serum Phosphate Unknown; Cystinosis												
–	5.5	+	+ pentose (?) lactose (?)	0	+	–	0	–	+	–	–	++++	Degeneration of tubular epithelium	Normal	+	
–	–	0.1%	1-2%	+	+	+	–	–	0	–	–	–	Degeneration of tubular epithelium; interstitial fibrosis	Focal necrosis	+	
				7. Rickets; No Glycosuria; Hypophosphatemia; Cystinosis (?)												
1.001-1.028	Acid-Alk.	Tr. ++++	0	+	+	+	–	–	±	–	+	..	.....	.....	..	Alive
1.001-1.030	Acid-Neutr.	+	0	+	+	+	–	–	–	–	+	..	.....	.....	..	Alive
				8. Rickets; No Glycosuria; Serum Phosphate Unknown; Cystinosis												
–	–	+	0	+	+	–	–	–	–	–	–	–	Acute, nonsuppurative nephritis	–	+	
–	–	–	0	–	–	–	–	–	–	–	–	–	Cloudy swelling; nonpurulent pyelonephritis; cystine stones in pelvis	–	+	
				9. Rickets; Glycosuria Unknown; Serum Phosphate Unknown; Cystinosis												
–	–	–	–	–	–	–	–	–	–	–	–	++++	Glomerular proliferation; tubules morphologically normal	Focal necrosis	+	
				10. No Rickets; Glycosuria Unknown or No Glycosuria; Serum Phosphate Unknown; Cystinosis												
–	–	–	–	–	–	–	–	–	–	–	–	0	–	–	+	
–	–	++++	0	–	–	–	–	–	–	–	–	0	Destruction of glomeruli; atrophy of tubules; interstitial fibrosis	Normal	+	
1.005	–	Tr.	–	–	–	–	–	–	–	–	–	0	Tubular atrophy and hypertrophy	Focal necrosis	+	

2. One case [41] of hypophosphatemic rickets with glycosuria in which autopsy disclosed crystals of cystine deposited within the reticulo-

40. Milkman's case (Milkman, L. A.: Pseudofractures [Hunger Osteopathy, Late Rickets, Osteomalacia], Am. J. Roentgenol. **24**:29 [July] 1930; Multiple Spontaneous Idiopathic Symmetrical Fractures, ibid. **32**:622 [Nov.] 1934) is not included because the skeletal lesions were focal and because the author ascribes the glycuresis which appeared during the course of the illness to diabetes mellitus. While the published data are not inconsistent with the interpretation that glycosuria was renal, they are not adequate to prove the point.

41. Russell, D. S., and Barrie, H. J.: Storage of Cystine in the Reticulo-Endothelial System and Its Association with Chronic Nephritis and Renal Rickets, Lancet **2**:899 (Oct. 17) 1936.

endothelial system throughout the body (this phenomenon is termed cystinosis).

3. Two cases [42] of hyperphosphatemic, glycosuric rickets in 1 of which no autopsy was made while in the other the anatomic findings, although informative in some respects, were inconclusive in others.

4. One case [43] in which rickets, hyperphosphatemia and glycosuria during life were found on anatomic examination to be associated with cystinosis; 1 case of cystinuria in the sister of the foregoing patient.

5. Eight cases [44] of glycosuric rickets in which neither was the serum inorganic phosphorus determined nor pathologic examination made.

6. Two cases [45] of glycosuric rickets in which information about the serum phosphorus is lacking but in which cystinosis was demonstrated.

7. Two cases [46] of hypophosphatemic rickets without glycosuria but with cystinuria as revealed by quantitative examination during life.

8. Two cases [47] of cystine rickets without glycosuria in which the serum phosphorus was not determined.

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42. Danis, P. G., and Rossen, J. A.: Renal Rickets, J. Pediat. **18**:103 (Jan.) 1941.

43. (*a*) Hottinger, A.: Ueber Cystin-Diathese, Ann. pædiat. **156**:257, 1941 (*b*) Roulet, F.: Das anatomische Bild der Cystinkrankheit mit Zwergwuchs, ibid. **156**:284, 1941. (*c*) Bürki, E.: Ueber Augenveränderungen bei der Cystinkrankheit, ibid. **156**:324, 1941. (*d*) Esser, E.: Zur Diagnose der Cystinkrankheit, ibid. **156**:344, 1941. (*e*) Freudenberg, E.: Knochenanalyse eines Falles von Cystinkrankheit, ibid. **156**:335, 1941.

44. (*a*) Fairbank, H. A. T., in discussion on Ashcroft, G. V.: Renal Rickets, J. Bone & Joint Surg. **8**:279 (April) 1926. (*b*) Hess, A. F.; Lewis, J. M., and Rivkin, H.: Newer Aspects of the Therapeutics of Viosterol (Irradiated Ergosterol), J. A. M. A. **94**:1885 (June 14) 1930. (*c*) Fornara, P.: Glicosuria normoglicemica (diabete renale) con nefrite e rachitismo renale e diabete vero con normoglicemia iniziale e glicosuria oscilante, Boll. d. Soc. ital. di pediat. **3**:187, 1935; (*d*) Considerazioni sopra un caso di "rachitismo renale" con nefrosi e glicosuria normoglicemica, Lattante **15**:457 (May) 1937. (*e*) Caussade, L.; Verain, M., and Neimann, N.: Sur trois variétés de nanisme rénal: 1. Nanisme rénal pur. 2. Forme associée au rachitisme ostéoclastique. 3. Forme associée à l'ictère hémolitique, Arch. de méd. d. enf. **43**:65 (March-April) 1940.

45. (*a*) Lignac, G. O. E.: Ueber Störung des Cystinstoffwechsels bei Kindern, Deutsches Arch. f. klin. Med. **145**:139, 1924; (*b*) Derangement of Cystine Metabolism in Children, Nederl. tijdschr. v. geneesk. **68**:2987 (June 28) 1924; (*c*) Deranged Cystine Metabolism in Children, ibid. **69**:819 (Aug. 15) 1925; (*d*) Ueber Erkrankungen (u. a. Nephrose und Nephritis) mit und durch Zystinablagerung in verschiedene Organe, Krankheitsforschung **2**:43, 1926; (*e*) Zystinbefunde bei einer bestimmten Kinderkrankheit, Verhandl. d. deutsch. path. Gesellsch. **21**:303, 1926. (*f*) Beumer, H., and Weppler, W.: Ueber die Cystinkrankheit der ersten Lebenszeit, Klin. Wchnschr. **16**:8 (Jan. 2) 1937.

46. Pache, H. D.: Ueber die Cystein-Cystinstoffwechselstörung der ersten Lebenszeit und ihre Beziehung zu Zwergwuchs und renaler Rachitis, Ztschr. f. Kinderh. **62**:1, 1940.

47. Lignac (footnote 45 *a*, *b*, *c*, *d* and *e*).

9. One case [48] of severe rickets which was not studied clinically but in which cystinosis was disclosed by necropsy.

10. Three cases [49] concerning which little is known except that rickets was apparently not present, glycuresis was absent or undetected and cystinosis was discovered at autopsy.

The foregoing arrangement of case material aims to draw attention to the existence of a relationship between rickets, nondiabetic glycosuria and cystinosis. It is the purpose of the following discussion to examine the association in order to supply a basis for more critical appraisal of the present case.

All in all, the number of instances of coincidence of rickets and glycosuria is not inconsiderable, 28 cases of such coincidence in infants and children having been found in a search which lays no claim to being exhaustive. To these may be added the 2 comparable cases of glycosuric osteoporosis in adults. Illustrations of the concurrence of rickets with cystinosis are not so numerous; 7 have been identified. In an additional case (Fanconi, case 1) it is possible to infer that cystine deposits were present. Since, as will be made clear, the recognition of cystinosis depends on necropsy, the disparity is to be expected. Pache interpreted the cystinuria in his 2 cases of nonglycosuric hypophosphatemic rickets to be synonymous with cystinosis. This correlation has not been proved. However, the fact that Lignac found cystine stones in the urinary tract in 1 of his 3 cases of cystinosis argues for the correctness of Pache's assumption.

That rickets, nondiabetic glycosuria and cystinosis can occur simultaneously in the same person is brought out by the fact that of 11 autopsies on patients with glycosuric rickets cystine deposits were recognized in 4, while their presence was suspected in a fifth (Fanconi, case 1). Failure to identify cystine in the other 6 patients is of uncertain significance for two reasons: First, the crystals are soluble in solution of formaldehyde and in other aqueous fixatives, tending to disappear from the specimens either before sections are cut or while they are being stained and mounted. There is reason to believe that this happened in Fanconi's first case; the case may accordingly be classified as an instance of probable cystinosis. Second, even when

48. Benoit, W.: Calcinosis universalis, Beitr. z. path. Anat. u. z. allg. Path. **94**:611, 1935.

49. (*a*) Abderhalden, E.: Familiäre Cystindiathese, Ztschr. f. physiol. Chem. **38**: 557, 1903. (*b*) Kaufmann, E.: Lehrbuch der spezielle pathologische Anatomie, ed. 7-8, Berlin, Walter De Gruyter & Co., 1922, vol. 2, p. 1107; Pathology for Students and Practitioners, translated by S. P. Riemann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 2, p. 1413. (*c*) Rössle, R.: Beiträge zur Frage der Speicherungskrankheiten, Verhandl. d. deutsch. path. Gesellsch. **31**:133, 1938. (*d*) Russell and Barrie.[41]

crystalline deposits have been evident, their chemical nature has sometimes been mistaken. Thus, both Benoit and Rössle have described as instances of calcinosis cases in which the condition was undoubtedly cystinosis. These reservations are not intended to imply the opinion that in all cases rickets with glycosuria is associated with accumulation of cystine in the tissues. However, it should be made clear that none of the reported cases constitutes an unassailable instance of the situation in which glycosuria and rickets are present yet cystinosis is absent.

The associations thus far described may be visualized in the following diagram (fig. 7) in which the linkage between rickets and glycosuria on the one hand and between rickets and cystinosis on the other is represented by the broken lines and the adjacent numerals, while the concatenation of the three is symbolized by the solid lines

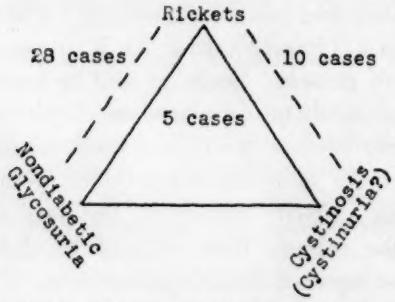

Fig. 7.—Associations between rickets, glycosuria and cystinosis.

forming a triangle which encloses the figure denoting the number of cases in which this combination has been realized.

It will be noted that no example of the combination of glycosuria and cystinosis without rickets has been recorded. Whether this indicates that the duad has not occurred or simply that it has not been recognized is uncertain. In the case of nonrachitic cystinosis reported by Russell and Barrie, the urine did not contain sugar. In the 2 cases described by Abderhalden and by Rössle, information on glycosuria is not available.

Concerning the type of rickets present in these cases, that is, whether the inorganic phosphorus of the serum was reduced or elevated, the material permits only three generalizations: First, glycosuric rickets can be associated both with hypophosphatemia and with hyperphosphatemia. The former is apparently more common than the latter, having been observed 15 times in children—plus 2 cases of hypophosphatemic osteoporosis in adults—while the latter is represented by only 3 cases. Second, both species of combinations may be further associated

with cystinosis. Each possibility, namely, hypophosphatemic, glycosuric rickets with cystinosis and hyperphosphatemic, glycosuric rickets with cystinosis, has been realized in a single case. Third, nonglycosuric, hypophosphatemic rickets may be correlated with cystine deposits. This is shown by 2 cases.

Since the 4 cases last referred to are the only ones in which information is available concerning all four points, quantitative analysis beyond that which has been essayed is not possible. At most it is hoped that we have conveyed the suggestion that the Fanconi syndrome, with its combination of rickets, hypophosphatemia, glycosuria and somewhat ambiguous anatomic substrate, is not a discrete constellation, but, on the contrary, that it merges without easily definable transition on the one side with nonglycosuric, hyperphosphatemic rickets, which

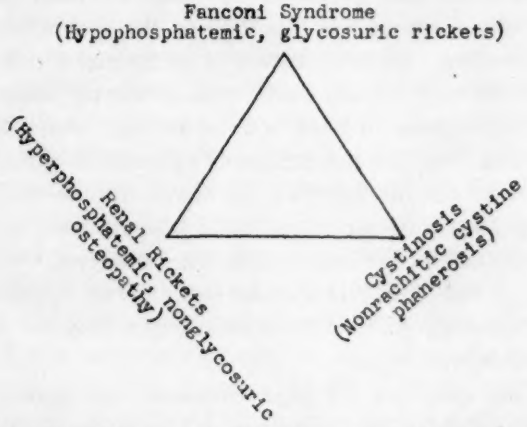

Fig. 8.—Associations between the Fanconi syndrome, hyperphosphatemic rickets and cystinosis.

has been commonly called renal rickets, and on the other with a group of conditions without rickets, the most distinctive feature of which is the deposition of crystalline cystine in the tissues. This relation, too, may be looked on as a triangular one, with the Fanconi syndrome at one apex, hyperphosphatemic rickets at the second, cystinosis at the third and the transitional forms occupying intermediate positions along the sides (fig. 8). Whether the relation thus postulated is fundamental or whether the apparent continuity exhibited by the forms is artificial cannot be decided from the evidence which is available at the present time.

ETIOLOGY

The defect of mineralization of the skeleton which characterizes the Fanconi syndrome and its homologues is not fundamentally due to lack of vitamin D. This is indicated by the presence of many features

which are not part of the familiar picture of infantile rickets; also by the more significant observation that treatment with conventional amounts of vitamin usually has no demonstrable effect, while the employment in several cases of doses which would be expected to accomplish significant if not permanent healing of "refractory" rickets has yielded, with 1 possible exception (Smyth), inconspicuous or ephemeral benefit. Warkany's [50] demonstration of a normal concentration of vitamin D in the blood serum of Guild's patient and the statement of Gittleman and Pincus that the concentration in the blood was slightly increased indicate that the lack of effect is not related to failure of absorption. Admittedly, these considerations do not exclude the possibility of interference by some metabolic fault with the activation of vitamin D. Evidence on this point is lacking.

It is conceivable that privation of other essential food elements may be responsible for one or another of the distinctive features of these cases. However, the combination of symptoms which they present does not simulate any known nutritional deficiency state. Moreover, the patients' diets appear to have been of average composition. Hence, it is probable that these are not deficiency syndromes. Infection, poisoning—such as that due to ingestion of heavy metals—and other categories of exogenous causes received little support from analysis of the case records. Attacks of febrile pyuria were observed by De Toni, by Fanconi and by van Creveld; Lignac encountered "pyelonephritis" at autopsy. Similar suggestion of infectious origin does not figure prominently in other reports.

Although the data are far from complete, the genetic features of the cases provide the most suggestive evidence concerning causation. Blood relationship between the parents and duplication of the syndrome in more than one member of the same generation have been encountered several times. Thus, in the cases of the Fanconi syndrome consanguinity has been recognized three times (De Toni; Fanconi, case 2, and McCune, Mason and Clarke) and suspected once in addition (Fanconi, case 3). The brother of one of Fanconi's patients and a sister of one of Russell and Barrie's patients died of an apparently similar disorder; a sister of Gittleman and Pincus' patient died at 10 months of age of rickets and pneumonia. The patients of Danis and Rossen, both of whom showed glycosuric rickets with hyperphosphatemia, were brother and sister. Hottinger demonstrated cystinuria in a sister of his subject who showed hyperphosphatemic, glycosuric

50. (*a*) Warkany, J.: Estimation of Vitamin D in Blood Serum, Am. J. Dis. Child. **52**:831 (Oct.) 1936. (*b*) Warkany, J., and Mabon, H. E.: Estimation of Vitamin D in Blood Serum: II. Level of Vitamin D in Human Blood Serums, ibid. **60**:606 (Sept.) 1940.

rickets and cystinosis. The same relationship existed between Pache's 2 patients who had nonglycosuric, hypophosphatemic rickets and cystinuria. Further background for the hereditary concept of causation is provided by the known genetic origin of nondiabetic glycosuria in some cases. Although a relation between cystinosis and hereditary cystinuria has not yet been proved, it is suspected to exist. This possibility supplies a final point of support for the hereditary causation of the syndromes under consideration.

PATHOLOGY

Postmortem examination has been made of 11 children who manifested glycosuric rickets during life. The amount of information available in the individual cases varies from Fairbank's cryptic statement that "autopsy showed the glycosuria to be renal, not pancreatic" to Sturzenegger's comprehensive report of the anatomic findings in Fanconi's first case and Roulet's detailed description of the pathologic features of Hottinger's case. In 5 instances (Schier and Stern; Russell and Barrie; Danis and Rossen; Fanconi, case 1; Lignac, case 1) microscopic features of rickets are described. It does not appear that in any instance the postmortem observations cast doubt on the correctness of the clinical diagnosis of the osseous disorder. Both Sturzenegger and Roulet described histologic changes characteristic of renal osteodystrophy: In addition to the presence of disarrangement of endochondral and periosteal ossification, typical of infantile rickets, there was also "dissection" of the secondary spongiosa and compacta by fibroblastic elements derived from the marrow. In the light of this observation, which is commonly interpreted to indicate hyperparathyroidism, it is surprising that in both cases the parathyroid glands were said to be normal in size. No mention was made of their histologic structure. The parathyroid glands were visibly enlarged in the cases of Schier and Stern and of Russell and Barrie; in the former there was an increase in the number of clear cells, while in the latter alteration of architecture was not conspicuous. Benoit, concerning whose case no clinical data are available, also described enlarged parathyroid glands of normal cellular makeup.

To clear the way for discussion of the anatomic features which possess greatest interest, it may be stated summarily that, although examination was made in several cases, in no instance were significant abnormalities identified in the hypophysis, thyroid, pancreas or adrenal glands.

Pathologic peculiarities of the kidneys have been recognized more consistently than any other lesion. Although Schier and Stern observed only a "honeycomb-like albuminous coagulum within the proximal and

distal convoluted tubules," the descriptions in the other cases are more informative. Van Creveld found the kidneys large and firm; although no obstruction was demonstrated, the ureters and pelves were dilated. The glomerular endothelium was of a cuboidal type; the tubules themselves were dilated and their epithelium flattened. In Fanconi's second case the changes were restricted to the basal stratum of the proximal convoluted tubules, where there was observed a deposit of fat in the form of fine droplets. Commenting on the unpublished findings in her own case. Dr. Guild wrote:[38f] ". . . while there was no tubular degeneration in the ordinary sense of the word, there were very queer changes in the tubules which were unquestionable but different as far as I can tell from any of the tubular changes previously described. The epithelial cells lining the tubules were in many places extremely large, practically blocking the lumen, but this was not a cloudy swelling type of enlargement." Russell and Barrie described extensive destruction of the renal parenchyma together with "remarkable fibrosis of uneven density." Many of the glomeruli had been obliterated. There was hypertrophy of the tubules "in a few small islands" together with atrophy of the tubular epithelium elsewhere. These 4 cases were clinically indistinguishable from one another in that they were all characterized by hypophosphatemic rickets with nondiabetic glycosuria. Hence, the presence of cystine crystals in the tissues of Russell and Barrie's patient takes on added significance.

The patients of Danis and Rossen differed from the foregoing patients only in that the inorganic phosphorus level of the serum was elevated rather than reduced. Autopsy in 1 case revealed reduction of glomeruli and interstitial fibrosis, along with swelling, pallor and vacuolation of the tubular epithelium. These changes were virtually duplicated by the features noted at autopsy in 1 of the clinically indistinguishable fraternal cases of Hottinger; in this case crystalline cystine was demonstrated in the tissues.

Only 2 autopsies have been recorded in the 8 cases of group 5, table 4. Fairbank's statement, already quoted, yields only indefinite information. Fanconi's first case has been relegated to this category because, first, the serum inorganic phosphorus was not determined and, second, the observations at autopsy as set forth in great detail by Sturzenegger contain an element of ambiguity. With reference to the first point, it may reasonably be assumed that the serum phosphate was low; the correctness of this inference is supported by the facts that the serum calcium level was normal and that the renal glomeruli were intact post mortem. But for this uncertainty, the case would properly be classified in group 1. Sturzenegger described dilatation of the tubules together with alternate flattening and swelling of the tubular

epithelium, features which are reminiscent of those observed by Guild. The source of difficulty in the interpretation of Sturzenegger's observations is the fact that the tubular epithelium presented the appearance of having previously contained some particulate foreign solid which had been extracted during fixation. Sturzenegger conceived that this might have been cystine but was prevented by lack of material from further investigating the possibility. In the cases of glycosuric rickets with cystinosis described by Lignac and by Beumer and Weppler the kidneys were similarly affected, the most conspicuous changes being situated in the tubular epithelium. Renal lesions were also present in the 2 additional cases of cystine rickets reported on by Lignac; these were summarized by the author as "acute nonsuppurative nephritis" in 1 instance and "nonpurulent pyelonephritis" in the other. In only 1 case of glycosuric rickets did necropsy fail to disclose renal tubular lesions: Benoit commented on the presence of proliferative changes in the capsular endothelium but implied that the tubular epithelium was of normal appearance.

With respect to the liver the observations are divergent. Van Creveld and Guild encountered cirrhosis; in Fanconi's second case the organ was friable and there was some degree of fatty infiltration. Focal necrosis was described by Russell and Barrie, Beumer and Weppler, Benoit, and Rössle. In these 4 instances cystinosis was also identified; it appears that the necrosis was of mechanical origin, due to encroachment of masses of crystals on the liver cells. The microscopic aspects of the liver were described as normal by Schier and Stern, Danis and Rossen, Hottinger, Lignac, and Russell and Barrie in their second case, of which cystinosis was also a feature. The significance of these observations will be touched on later.

CLINICAL FEATURES

The manifestations of the Fanconi syndrome and related disorders usually make their appearance during the first two years of life; the occasional recognition of symptoms between the second and the sixth month suggests that in some cases, perhaps, all, the condition is congenital. Retarded development, appearance of rickets and loss of appetite are early features. Periods of progression alternating with remissions lead to dwarfism and physical deformity. Acute gastrointestinal disturbances, episodes of dehydration and bouts of unexplained fever punctuate the course.

Nondiabetic glycosuria has been identified during infancy in several cases but has escaped notice until childhood in others; the concentration of reducing substance can vary between a trace and 4 or 5 per cent. In most cases it has been shown beyond doubt that the glycosuria was of renal origin. Danis and Rossen implied that the phenomenon was due to mild diabetes mellitus in their fraternal patients; the evidence

which they presented does not justify this interpretation. The elimination of sugar is characteristically continuous, at least in patients with the more severe forms of the syndrome; in some it has been intermittent, disappearing for considerable periods of time. This has been noted to occur with special frequency just before death. Fanconi and others have shown the reducing substance to be dextrose; many have assumed its identity. Lignac's patient first excreted a pentose and later a substance the osazone of which melted at the temperature of lactosazone. In view of the absence of digestive disturbances, this unique inconsistency remains unexplained. Gittleman and Pincus reported "dextrose and fructose in nearly equal concentrations" but did not describe the technic of identification. Van Creveld ascribed part of the reducing capacity of his patient's urine to glycuronic acid; dextrose was also present in concentrations which varied from 1 to 2 per cent.

The fasting blood sugar exhibits noteworthy variability, not only in different cases but at different times in the same case. Table 4 contains values as low as 48 mg. per hundred cubic centimeters and others as high as 160 mg. It will be seen that the variability within the group as a whole is no greater than that shown by the same patient at different times. The reported tests of the dextrose tolerance are based on such a variety of technics that their appraisal is unsatisfactory. The broadest permissible generalization is that many of the curves show a sharp rise to high levels followed by a rather slow decline to values that are frequently hypoglycemic. Although in some cases the form of the curve has been suggestive of diabetes, in no instance have all the characteristic features of diabetes mellitus been realized. Glycosuria varies in intensity with changing levels of blood sugar but is characteristically present at all times, even when the blood sugar is low.

Both Debré and Fanconi witnessed symptoms of what Fanconi termed "hyperglycemic shock" in conjunction with the oral administration of dextrose for test purposes. Debré's patient became restless and pallid and then lapsed into fatal coma. Fanconi's second and third patients were rendered extremely uncomfortable but survived. Others do not seem to have shared this experience.

In most cases the volume of the urine has been moderately increased; in these and in others in which the urinary volume was not measured polydipsia has been noted. In Fanconi's third case there was diversion of water to the urine at the expense of the insensible perspiration. It was noted that our patient sweated little even during the hottest part of the summer. It may be surmised that the attacks of unexplained fever bear a relation to dehydration.

Despite the large volume of urine, the specific gravity has frequently been reported to be high. This is probably due in part to the presence of sugar and protein and in part to the presence of other solutes, which will be discussed presently.

Albuminuria of moderate degree is a consistent phenomenon; casts, leukocytes and epithelial cells are often present. Microscopic hematuria has been reported occasionally.

These features, viewed in the light of the postmortem aspects of the cases, prompt interest in the functional state of the kidneys. In the majority of instances characterized by hypophosphatemia the total nonprotein nitrogen and the urea of the blood have been found to be normal or only slightly increased, except during the agonal period, when hyperazotemia has been observed several times. These conditions reflect normal glomerular filtration. In the hyperphosphatemic patients of Danis and Rossen and of Hottinger there was considerable retention of nitrogen. Hottinger's patient showed cystinosis. The state of other elements of renal function will be touched on in the course of the following discussion.

Table 4 lists 30 cases of glycosuric rickets or osteomalacia. In 20 cases information is available concerning the inorganic phosphate level of the serum. In 17 of these there was hypophosphatemia, with concentrations of from 1 (Fanconi, case 2) to 3 mg. (Russell and Barrie) per hundred cubic centimeters; thus these cases fulfilled the requirements for classification as instances of the Fanconi syndrome. In 1 of these cases (Russell and Barrie) there was associated cystinosis. In 3 cases (Danis and Rossen, and Hottinger) the serum phosphate was elevated to concentrations as high as 9.5 mg. This feature, together with elevation of nonprotein nitrogen, constitutes the only essential difference between these cases and the others. In 1 of them, too, cystinosis was present (Hottinger).

In patients with hypophosphatemia the serum calcium has usually been found to be normal or only slightly reduced. However, concentrations as low as 8 mg. per hundred cubic centimeters were encountered by Fanconi and by Guild; in Fanconi's case there was tetany. In the cases distinguished by hyperphosphatemia the serum calcium has shown slight to extreme reduction; in 3 cases there were attacks of tetany at one time or another. In formulating these generalizations we have dismissed as implausible the value of 17.6 mg. reported by Goldmann and Ekstein and that of "4.582 mg." supplied by Fornara.

Reduced carbon dioxide–combining capacity and a reduced bicarbonate content of the serum have been observed so frequently that diminished alkali reserve appears to be a characteristic feature of the more severe types of the disease. Values of 30 volumes per cent are common, with extremes of 28 and 52 volumes. Acceptable values for the serum p_H have not been published.

The features of the disturbance of the cation-anion equilibrium which is indicated by these observations have not been satisfactorily

described. Hottinger's relatively complete data on the electrolyte structure of the serum were obtained from a dying child and cannot be accepted as representative. Guild, and Gittleman and Pincus found the sum of the cations to be within normal limits. Our own results, which we put forward diffidently since they were not confirmed, indicate only a slight reduction of sodium and fixed base. Taken at their face value, these observations point to an increase of mineral or organic anions.[51] The slight elevation of chloride, which was noted by Guild, by Gittleman and Pincus and by us, does not alone account for the discrepancy. Caussade's report of a chloride concentration of 125 milliequivalents has not been duplicated. The serum phosphorus has been reduced more frequently than not; even in cases in which the concentration has been found higher than normal, the elevation has not been great enough to displace significant amounts of bicarbonate. Protein and its fractions have been found invariably to be normal. No determinations of sulfate are available.

The foregoing considerations lead to the expectation of an elevated concentration of organic acids in the blood serum. Guild's single attempt to verify this possibility led to results which were considered as suggestive but equivocal. Gittleman and Pincus found 11.3 and 9 mg. of acetone bodies per hundred cubic centimeters of blood on two occasions. They reported normal values for lactic acid. No measurements of amino acids have been reported. The approximately normal concentration of the nonprotein nitrogen of the whole blood and serum suggests that if an increase of amino acids is ever present it must be small. This inference is strengthened in our case, in which the urea fraction of the nonprotein nitrogen was also normal.

Despite the demands made by acidosis, the p_H of the urine has frequently been observed to be above 6.5 and higher. However, Schier and Stern recorded a minimum value of 5.3, and in our case the index occasionally assumed values of 4.8, demonstrating that the restriction of acidity and the renal functional defect which it connotes are not always present.

High urinary concentration of ammonia has been encountered whenever the examination has been made. This is true of the cases characterized by comparatively neutral urine as well as in the 2 cases just cited, in which the degree of acidity approached the physiologic maximum.

The titrable acidity of the urine in Fanconi's third case was high, attaining levels of from 0.2 to 0.5 milliequivalents per kilogram of body weight daily, despite the fact that the p_H of the urine was only 7.13.

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51. Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid: A Lecture Syllabus, ed. 3, Boston, Spaulding Moss Co., 1941.

This implies exaggerated excretion of buffer substances. In our own case, in which low urinary p_H complemented the excretion of buffer, the titrable acid reached extraordinary proportions, amounting from 1 to 2.5 milliequivalents per kilogram per day on several occasions.

The buffers which are responsible for this phenomenon are phosphate and organic acids. Fanconi was impressed by the intensity of the phosphaturia manifested by 1 of his patients. Although the data of his balance study do not clearly justify the emphasis which he laid on this point and although Goldmann and Ekstein found the urinary phosphorus to be reduced, Fanconi's contention is supported by the observations of Guild and by our own. It is confirmed in a striking way by the observations of Gittleman and Pincus. Their data reveal that the urinary phosphorus varied from 76 to 121 per cent of the net absorbed phosphorus. These comments and their possible corollaries apply only to the cases characterized by hypophosphatemia. No information on this score is available concerning the cases in which increased concentrations of serum phosphate have been recorded.

Exaggerated excretion of organic acids was first reported by Debré; the output was described as "much increased." This observation has been confirmed by Fanconi, who measured a daily excretion which varied between 3.3 and 5.3 milliequivalents per kilogram; by Guild, whose patient voided approximately twenty times the normal amount of organic acid; by Goldmann and Ekstein, who, if we correctly decipher their notation, found the excretion to fluctuate between 30 and 40 milliequivalents per kilogram per day, and finally by our own observations, which have shown a daily elimination of from 4 to 20 milliequivalents per kilogram. The mean twenty-four hour output of a healthy person may be taken as approximately 1 milliequivalent per kilogram.

Fanconi suspected that the organic acids might belong to the amino acid series. Our confirmatory observations are the first to be recorded. In no instance have crystals of amino acids been found in the urine prior to chemical treatment of the specimen. The mixture in our case appeared to contain the acids which one would expect to recover from the catabolism of the protein of a normal mixed diet; none were present in disproportionate amount. Hottinger failed to isolate cystine from the urine of his patient, who was subsequently shown to have cystine storage in the tissues. He did, however, recover cystine and possibly cysteine from the urine of a healthy sister of the patient. Pache reported what he considered to be pathologic amounts of cystine in the urine of his 2 fraternal patients.

Balance studies of the mineral metabolism have been made by Fanconi, Goldmann and Ekstein, Gittleman and Pincus and us.

Fanconi found a heavy net loss of nitrogen, phosphorus and calcium along with an excessively negative balance for potassium. This was at least in part explained by concurrent loss of weight and the presence of fever. The exchange of sodium and chlorine was in virtual equilibrium. The daily excretion of 0.24 Gm. of phosphorus in the urine was conspicuously high in relation to the intake of 0.45 Gm. That which appeared in the urine constituted 124 per cent of the net absorbed phosphorus. Despite the fact that the amount of calcium in the feces exceeded the amount contained in the diet, it is surprising that the urine carried only 0.009 Gm. in twenty-four hours, about 2 per cent of the amount excreted.

The details of Guild's study are not available. It is known only that "a metabolism study showed a negative balance for calcium and phosphorus" and that "the urinary phosphorus was relatively high."

Goldmann and Ekstein found a negative balance for phosphorus before treatment. The amount in the feces exceeded that ingested. In spite of this circumstance, relatively large amounts were excreted in the urine. The balance for potassium was slightly positive; there was marked retention of sodium and chlorine. It is reported that under the influence of a 40 per cent increase of dietary potassium, phenomenally increased retention of mineral took place: This reached 90 per cent of the amount of phosphorus ingested, 60 per cent of calcium and 87 per cent of potassium.

The admirable studies of Gittleman and Pincus, which extended over a period of five months, demonstrated positive balance for nitrogen, sodium, chlorine and magnesium and throughout most of the study for potassium. The observations with relation to phosphorus are of particular interest: Hyperphosphaturia persisted throughout the entire period of observation. In the beginning the phosphorus excreted in the urine amounted to 120 per cent of the net absorbed phosphorus. The administration of approximately 6,000 U. S. P. units of vitamin D (as vitamin D_2, calciferol) daily, first alone and then in combination with 15 millimols of orthophosphoric acid, reduced the urinary loss to 80 per cent of the net absorbed phosphorus. This effect was the result of both improved absorption from the alimentary tract and diminished urinary output. The serum phosphate rose from 1.8 to 2.6 mg. per hundred cubic centimeters, and evidence of incipient healing was present in roentgenograms. However, the improvement was not maintained. Subsequently, by the use of dicalcium phosphate, first alone and then in combination with vitamin D, the urinary excretion of phosphorus was reduced to 65 per cent of the net absorbed amount. The experiment was not continued long enough to appraise the ultimate value of this treatment.

PROGNOSIS

The outlook for infants and children who manifest glycosuric rickets is poor but not unqualifiedly bad. Of the 28 juvenile patients who are included in the first six categories of table 4, 16 had died before their cases were reported on, 9 were alive and the fate of 3 remains unknown. The reports of Smyth, of Goldmann and Ekstein and of Gittleman and Pincus contain a note of optimism. The cases of adults described by Hunter convey a similar implication regarding survival. The prognosis for full functional efficiency appears to be less hopeful. Too little is known about cystinosis, either in general or in its relation to the Fanconi syndrome, to permit a statement on prognosis. The difficulties of recognizing its presence during life are considerable.

TREATMENT

Of the variegated modes of therapy which have been tried only three require comment. Insulin has been used several times without curative results. Lignac ascribed temporary improvement to its use; Gittleman and Pincus reported relief of ketosis.

In view of the frequency of reduction of serum bicarbonate, of ketosis and of increased urinary excretion of organic acids, especial interest attaches to the results of alkali therapy. Debré used sodium bicarbonate fruitlessly to treat his patient, who became comatose during the course of a dextrose tolerance test. Guild attempted to combat acidosis with sodium bicarbonate and sodium lactate; no benefit was evident, and the effort had to be abandoned because of the development of drowsiness and distention. Fanconi's use of a "strongly alkalinizing diet," as reported on by Sturzenegger, appears to have had a temporarily beneficial effect. Gittleman and Pincus reported failure with the administration of citric acid–sodium citrate buffer mixture in amounts of 60 cc. daily for three months. By contrast, the advantage which Goldmann and Ekstein ascribed to a diet said to be high in potassium appears phenomenal. Danis and Rossen also ascribed favorable results to this measure.

Vitamin D is said to be ineffective in controlling the rickets which constitutes part of the Fanconi syndrome and related conditions. This statement is true in relation to the effectiveness of amounts ordinarily used in prophylaxis and treatment. However, Guild succeeded in raising the level of inorganic phosphorus in the serum slightly and producing some calcification of the skeleton by the use of large doses. The experience of Gittleman and Pincus demonstrated that vitamin D is not entirely without effect; it is to be regretted that they did not investigate the consequences of larger doses. Smyth obtained complete healing of rickets with 50,000 U. S. P. units of vitamin D daily

employed over an extended period of time. There was transient increase of phosphate in the serum of Pache's patient after he received a single large dose of vitamin D by mouth. The rise was not well sustained, and healing was not evident in the roentgenograms. This matter requires further investigation.

COMMENT

Called on to explain the pathogenesis of a group of cases characterized by rickets, glycosuria, hypophosphatemia and normoazotemia, Fanconi conceived the hypothesis that the syndrome which bears his name is the expression of a genetically grounded anomaly of the structure and function of the tubular portion of the kidneys. To infection he assigned a role of subordinate importance as a possible activating factor. He specified that the functional peculiarity consists in impaired capacity of the tubular epithelium to resorb certain solutes from the glomerular filtrate. Thus glycosuria was regarded as due to failure to retain dextrose and the alkalinity of the urine, a conspicuous feature of his case, to defective resorption of cations. The inability of the kidneys to produce urine of requisite acidity was partly compensated by increased formation of ammonia, partly by exaggerated excretion of phosphate at a p_H only slightly lower than that of the body fluids and partly by increased volume of urine. Inasmuch as compensation was incomplete, an intermediary acidosis—presumably due to accumulation of inorganic anions—ensued; this, in turn, led to excessive production and excretion of organic acids. Lacking experience with cases in which hyperphosphatemia and hyperazotemia replaced hypophosphatemia and normoazotemia, Fanconi demarcated his cases sharply from those of classic renal rickets. Cases had not yet been reported on which entitled him to suspect a relation between nephrogenous rickets and cystinosis.

As has been indicated, we are disposed to agree with Fanconi in assigning to the kidney the part of principal importance in the pathogenesis of the disturbance of metabolism and calcification present in these cases. However, the concept that inability to elaborate an acid urine is the critical feature of the dysfunction in all cases is not supported by the evidence.

With respect to treatment, considerable practical importance attaches to the correctness or incorrectness of Fanconi's conjecture that acidosis depends on deficient tubular resorption of "basic valences." Disturbance of electroneutrality of the body fluids due to diabetes of exogenous cations should be at least temporarily rectifiable by treatment with alkali, while if the deficit represented principally anions acid would be required. Furthermore, although it is unlikely that defect of resorption would involve one type of positively or negatively charged ions to the exclusion of others, it may be suspected that one species might be more

seriously affected than others. Hence, in order to design effective treatment it is necessary to know not only whether acid or base is squandered but also which particular anion or cation is most subject to waste.

We have cited data which disprove the existence of a serious defect of the sodium-sparing mechanism. In addition, the balance studies of Fanconi and of Gittleman and Pincus and our own failed to demonstrate conspicuous loss of sodium in the urine. The results of the last two studies also exonerate magnesium.

The evidence which relates to the possibility of a lowered renal threshold for calcium is conflicting. The balance studies of Fanconi and of Goldmann and Ekstein did not show striking loss of calcium in the urine. On the other hand, our study and that of Gittleman and Pincus disclosed a degree of hypercalciuria which was large when viewed in relation to the state of demineralization of the skeleton. This may be interpreted in one of three ways: as an expression of renal tubular incompetence, as an indication of increased requirement of cation to neutralize urinary acids or as a manifestation of compensatory hyperparathyroidism. Present evidence does not permit final choice among these alternatives.

There is conflict, too, concerning the importance of loss of potassium. Against the therapeutic benefits claimed by Goldmann and Ekstein and Danis and Rossen must be set the normal values for potassium balance obtained by Gittleman and Pincus. The excess of urinary potassium which Fanconi demonstrated was accompanied by negative nitrogen balance and was quite properly ascribed to the presence of an episode of acute illness characterized by fever and loss of weight.

This evidence has persuaded us that defect of resorption of cation is not the point of principal importance. Comparable considerations, which will not be reviewed in detail, disavow the existence of tubular incompetence with relation to the conservation of bicarbonate and chlorine. Information is lacking concerning the metabolism of sulfur and sulfate. Phosphorus and organic acids remain to be discussed.

Among the cases under consideration, in those which are instances of the Fanconi syndrome there is hypophosphatemia; the only evident difference between these and certain others is that the latter are characterized by elevation of the serum phosphate and nonprotein nitrogen. Of the several possibilities which may be called on to account for hyperphosphatemia, that of reduced glomerular filtration is the most acceptable. With regard to hypophosphatemia, the observations which have been cited leave no room for doubt that reduced tubular resorption is the responsible mechanism. As in the case of calcium three explanations must be considered, namely, acidosis, hyperparathyroidism

and inherent tubular incompetence. The accessory clinical data and the anatomic findings appear to favor the last.

It is evident that the small number of data at our disposal are not sufficient to make clear the reason for the increased amount of organic acids in the urine of 4 patients.[52] With relation to the hyperaminoaciduria suspected in Fanconi's patient and demonstrated to exist in ours, the absence of unequivocal increase of concentration in the blood conveys the implication that the phenomenon may be due to defect of tubular resorption. However, the possibility of hyperaminoacidemia in some subjects cannot be denied. Furthermore, the occurrence of cystinosis implies at least local increase of concentration of the compound. Ketonuria and lacticaciduria are doubtless related to recurrent hypoglycemia and in some cases to hepatic damage. Until further studies have been made, their significance must remain entirely speculative.

We must confess inability to suggest more than two speculative propositions which include generalized cystinosis as one of their elements: First, prolonged renal waste of essential metabolites may be conceived to lead to a disturbance of cystine metabolism, with the result that cystine is deposited in the tissues instead of undergoing oxidation to sulfate and excretion by the kidneys; second, it is possible that the conditions of the type under consideration which are characterized by cystinosis represent an etiologically independent entity in which the deposit of an insoluble substance within the kidneys leads to both glomerular and tubular damage of varying severity and relative degree, producing thereby the chain of consequences which constitute the Fanconi syndrome and its congeners.

SUMMARY

The present report describes a case of severe hypophosphatemic rickets associated with renal glycosuria and extreme reduction of the bicarbonate in the serum of a 9 year old boy. Although moderate polyuria, albuminuria and cylindruria were detected, the nonprotein nitrogen and urea were normal. The urine was acid and contained exaggerated amounts of ammonia and organic acids. Of these 82 per cent were amino acids, 11 per cent lactic acid and 7 per cent beta-hydroxybutyric acid. Slight reduction of fixed base and sodium in the serum was demonstrated. A balance study revealed excessive excretion of phosphorus and calcium by the kidneys. The metabolism of sodium, chlorine and magnesium appeared to be unaffected. Treatment with 5,000 U. S. P. units of vitamin D daily for several weeks had no

52. Debré and others.[38c] Guild, Pierce and Lilienthal.[38e] Goldmann and Ekstein.[38k] Fanconi.[12c]

obvious effect; other therapeutic recommendations were not carried out. The patient died; autopsy was not made.

The data were interpreted to indicate diminished ability of the renal tubular epithelium to resorb dextrose, amino acids and phosphate from the glomerular filtrate. Inasmuch as the requirement of cation to neutralize the organic acids was not met by the production of a highly acid urine, large amounts of ammonia and increased urinary volume, mineral cations of the body fluids were called on, with resultant depletion of fixed base. Recurrent hypoglycemia was thought to be responsible for the excretion of betahydroxybutyric acid. The presence of lactic acid was ascribed hypothetically to either renal tubular or hepatic dyscrasia.

The literature of the last fifteen years contains references to or detailed descriptions of 28 cases which are comparable with the foregoing so far as they were characterized by rickets and renal glycosuria, and 2 cases in which rickets was replaced by osteoporosis in adults. Hypophosphatemia was demonstrated in 17 of these cases; in 3 the serum phosphate was elevated; in 10 it was not determined. Associated manifestations similar to those exemplified by our patient have been recorded in the more recently published cases. In 5 instances, including our case, exaggerated urinary excretion of organic acids has been recognized but their identification has not been previously accomplished.

Eleven autopsies have been made on subjects of this group. Pathologic changes have been encountered most consistently in the kidneys. Here usually the renal tubular epithelium and less commonly the glomeruli have been found to be seriously affected. In a few cases the liver has shown changes varying in severity from focal necrosis to cirrhosis. In 4 cases deposits of crystalline cystine have been encountered within the reticuloendothelial system throughout the body. This phenomenon is designated cystinosis. There is circumstantial evidence to suggest that similar deposits may have been present in a fifth case. In view of the difficulty of preserving cystine crystals in sections of tissue prepared in the usual ways, it may be suspected that cystinosis has been overlooked in other cases.

On the basis of a larger personal experience than ours but with less material for critical analysis at his disposal, Fanconi conceived an explanatory hypothesis which ascribed to the kidney the primary role in the production of symptoms. Specifically, he postulated that nephrogenous dissipation of dextrose and cations, due to hereditary inadequacy of the tubular epithelium, was the critical feature of the syndrome which bears his name.

A review of the literature at the present time supports the concept of the central role of the kidneys in the pathogenesis both of the Fan-

coni syndrome and of allied disorders; interpretation of the significance of the hepatic damage which some patients exhibit requires further evidence. However, critical examination of the data of our own case and of others which have been reported indicates that renal tubular resorption of phosphorus is more seriously compromised than that of cation. This distinction has an important bearing on treatment. Finally, it is apparent that the Fanconi syndrome, with its combination of rickets, hypophosphatemia and renal glycosuria, is not a sharply definable clinical entity. On the contrary, it appears to be one phase, or aspect, of a larger morbid species and merges without perceptible demarcation on the one side with classic hyperphosphatemic renal rickets and on the other with the poorly understood process which is currently called cystine rickets.

APPENDIX

ABSTRACTS OF PREVIOUSLY REPORTED CASES OF THE FANCONI SYNDROME AND ALLIED DISORDERS

Inasmuch as the number of published observations is still small and many of the original reports difficult to procure, it appears warranted to submit a synopsis of the cases which have been encountered in a search of the literature on the subject. The most significant of the data derived from these abstracts are outlined in table 4.

ABDERHALDEN, 1903.[49a, b]—A 21 month old Swiss boy, the child of nonconsanguineous parents, died of inanition. Autopsy, which was carried out by Kaufmann,[49b] revealed an accumulation of round and angular crystals throughout the body. Chemical examination of the spleen, in which the deposits were heaviest, demonstrated that the crystals were composed of cystine. A survey of the family established the existence of cystinuria in the boy's paternal grandfather, his father and 2 brothers. It was learned that a third brother and a sister had died in infancy under circumstances similar to those which preceded the boy's death. The urine of the mother and of the grandmother was found to contain no cystine.

Kaufmann's brief description of the pathologic changes fails to mention the skeleton and kidneys. Years later Roulet [43b] searched the autopsy records at Basel, Switzerland, but failed to find the protocol.

LIGNAC, 1924.[47]—The first patient was a 3 year old boy, the only child of healthy parents. He had stopped growing at 1 year and never learned to walk. Although his appetite had long been poor, the child clamored incessantly for water and voided frequently. It was reported that he had been subject to frequent attacks of unexplained fever and that at some time in the past sugar had been detected in the urine.

The child was severely undernourished and extremely rickety. The urine had a p_H of 5.5 and an ammonia coefficient of 2.2 and contained protein, sugar, acetone, diacetic acid and a few leukocytes. The reducing substance was first identified as pentose and later as lactose; the second identification was based on the crystalline structure and the melting point of the osazone. At no time did the blood sugar exceed 156 mg. per hundred cubic centimeters.

Insulin was tried with temporary benefit. After a month fever, loss of appetite and vomiting recurred; casts appeared in the urine. Three months later the boy died.

Anatomic examination confirmed the rachitic character of the skeletal deformities. The spleen and liver were not enlarged. Diffusely disseminated deposits of crystalline cystine were demonstrated in the spleen, liver, kidneys, mesenteric lymph nodes and intestinal and pulmonary connective tissue and in the choroid plexus. In these locations the crystals were situated both within the cells and between them. Phagocytosis of the crystals by leukocytes and their inclusion in the reticuloendothelial cells were observed repeatedly. Deposits were not encountered in the pancreas, the thyroid or adrenal glands, the hypophysis or the brain. Best's carmine technic showed diminished glycogen content of the liver and kidneys. The epithelium of the proximal and distal convoluted tubules exhibited severe albuminous degeneration, characterized as nephrotic. The parenchyma of other organs showed no pathologic alterations.

Lignac's second patient, a 2 year old boy, had been undernourished "since birth." The mother was known to have severe kidney trouble, and a sister was small and sickly. Severe rickets was present. The urine contained 1.2 Gm. of albumin per liter, leukocytes and casts but no sugar. The systolic blood pressure was 92 mm. of mercury. Autopsy brought to light the presence of pleurisy, pyelitis and otitis media. Cystine crystals were found in all organs which were examined. They were especially numerous in the spleen. The kidneys were pale and swollen, and the cortex was gray. Microscopic examination disclosed evidence of acute, possibly pyelogenous, nonsuppurative nephritis.

The third patient, a girl, was 14 months of age. At 3 months she had had meningitis followed by hydrocephalus. The child had rickets. The urine did not contain sugar. In this case, too, all organs examined contained crystalline cystine. The kidneys were pale and swollen, and the cortex was gray; on the left side there was cloudy swelling of the parenchyma and on the right evidence of nonpurulent pyelonephritis. The left renal pelvis contained a cystine stone the size of a grape; about 1 cm. above the bladder in the right ureter was a cystine stone, which had produced mild hydronephrosis.

FAIRBANK, 1926.[44a]—In discussing a paper on renal rickets, Fairbank stated briefly that he had encountered 2 cases of renal dwarfism stigmatized by glycosuria. The first patient's condition was regarded to be of pancreatic origin. The second patient, a girl of 12 years, showed rickety changes in the bones with severe osseous deformity and juxtaepiphysial fractures. In the second case "autopsy revealed that the glycosuria was renal, not pancreatic."

SCHIER AND STERN, 1926.[38a]—The patient, a boy, was born four weeks before term, weighing 2,200 Gm. The mother suffered from epilepsy; whether or not the parents were consanguineous is not stated. He was fed at breast for one month and then on cow's milk. Supplementary vitamin D was not provided. At 2 months of age rickets became apparent and progressed thereafter. Treatment with a variety of agents, including phosphorized cod liver oil and exposure to sunlight, produced roentgen evidence of healing but accomplished little change in the physical manifestations of rickets. When the infant was 6 months old, the inorganic phosphorus content of the serum was 1.2 mg. per hundred cubic centimeters. At 8 months visible enlargement of the ends of the long bones developed in addition to the craniotabes and the rickety rosary already present; the serum phosphorus remained at 1.2 mg. Although the child had developed adequately up to 8 months, henceforth his weight and length remained stationary.

At 13 months glycosuria was detected; whether or not it had been looked for earlier is not clear. During the next four months the excretion of sugar, which was at first somewhat variable, increased in amount to as much as 9 Gm. daily and in concentration to as high as 3.5 per cent. Acetone and diacetic acid were occasionally present in low concentration. The glycosuria was shown to be renal. Fasting blood sugar values varied between 90 and 135 mg. per hundred cubic centimeters; ingestion of carbohydrate did not increase the blood sugar content to more than 150 mg. per hundred cubic centimeters but did result in increased excretion of sugar. On several occasions injections of epinephrine hydrochloride in amounts of from 0.1 to 0.5 mg. both intramuscularly and by vein raised the blood sugar from fasting levels of approximately 100 mg. to between 150 and 200 mg. at the end of thirty minutes, whence it fell to approximately normal values within three hours. The response was not dissimilar to that of a healthy child. The effect of insulin was not investigated.

During the last few months of life the deformities due to rickets became more severe; at 18 months the child had only three teeth. Although the serum calcium remained between 10.8 and 12.3 mg. per hundred cubic centimeters, the serum inorganic phosphorus continued at low levels, showing only small deviation from the value 1.7 mg. per hundred cubic centimeters. The rickets was not demonstrably influenced by exposure to noonday sunlight for as long as one hour daily, nor by the use of phosphorized cod liver oil or of hormocutan or by other measures.

The systolic blood pressure was somewhat elevated, to between 120 and 130 mm. of mercury; the pulse rate varied between 120 and 140 beats per minute at rest. The urine was highly acid for a time, with a p_H of 5.3; less acid values, of 6.3, 6.6 and 7.0, were obtained as the disease progressed and the amount of urinary sugar increased. The presence or absence of albuminuria and the character of the urinary sediment were not commented on. Urinary excretion of ammonia and diastase was increased. The child suffered many infections. He died suddenly when he was 18 months old.

Autopsy revealed the gross and microscopic conditions of severe rickets. Bronchopneumonia was present. In the lumen of the straight and convoluted tubules a coagulum was present; pathologic alteration of the tubular epithelium was not described. The liver cells contained an unusually small amount of fat but apparently were otherwise normal. The parathyroid bodies were definitely enlarged, although not to the degree characteristic of most cases of rickets of lesser severity. The superior parathyroid glands contained clear vesicular cells; in the inferior glands the parenchyma was normal. The other organs, including the pancreas, were also normal.

Boyd, 1927 [1a] and 1928 [1b]; Boyd and Stearns, 1941.[1c]—Nearly fifteen years ago in a pioneering although brief survey of diverse types of metabolic rickets Boyd alluded to cases characterized by atypical diabetes mellitus. These cases were published in detail in 1941.

The first patient, a 7 year old white girl of Polish parentage, had been fed at breast until 1 year of age; she had not received cod liver oil but had been exposed to sunlight for significant periods. She walked at 4 years. Fracture of a leg occurred shortly thereafter.

The child was small, 88 cm. in length, and weighed 14 Kg. The deformities and roentgen features of active rickets were present. There was evidence of chronic infection of the respiratory tract. Although the abdomen was prominent, it appears that the liver was not enlarged.

During the fourth month of observation glycosuria and ketonuria were discovered. The excretion of reducing substance varied between 15 and 94 Gm. per day; the amount of ketones ranged as high as 3.9 Gm. of acetoacetic acid daily. Other aspects of urinalysis were not reported.

The serum calcium varied between 8.2 and 12.0 mg., the inorganic phosphorus between 1.5 and 5.9 mg., and the carbon dioxide-combining power between 22 and 49 volumes per cent. The fasting blood sugar was between 48 and 103 mg. per hundred cubic centimeters; the values after ingestion of food varied between 123 and 250 mg. The nonprotein nitrogen was found to be normal on one occasion. Glycosuria was clearly renal.

Ketosis and acidosis were not affected significantly by the use of insulin or the administration of sodium bicarbonate by mouth. Three months of vigorous treatment with cod liver oil and ultraviolet rays produced ephemeral elevation of the serum phosphorus. Apparently the rickets showed no tendency to heal and was still active when the child died of bronchopneumonia, seven months after medical aid was first sought. There was no necropsy.

Boyd's second patient was a 2½ year old boy who had presented evidence of severe rickets since early infancy. The diet had at all times been extremely deficient. The patient weighed 7 Kg.

The urine contained 2 per cent of sugar. The calcium content of the serum varied between 8.5 and 9.2 mg.; the inorganic phosphorus content, between 1.3 and 2.0 mg., and the carbon dioxide-combining power, between 52 and 63 volumes per cent. The nonprotein nitrogen was 53 mg., and the sugar (whole blood) was measured once to be 90 mg. and thrice 120 mg. per hundred cubic centimeters. The glycosuria was presumably renal.

Administration of cod liver oil and the use of ultraviolet irradiation daily for one month produced no improvement. The child became marantic and died six weeks after entering the hospital. There was no autopsy.

HESS, LEWIS AND RIVKIN, 1930.[44b]—"We may add that we have recently seen an instance of what may be termed 'diabetic rickets,' which likewise showed an exceptional resistance to this form of medication [viosterol. AUTHORS.] This type of endogenous rickets is exceedingly rare; we have encountered only three cases in the course of a clinical experience of many years."

FANCONI, 1931.[18a]—Fanconi's first case was reported briefly in 1931. The abstract will be found with the detailed presentation of 3 cases reported on in 1936.

DETONI, 1933.[38b]—The patient was a 4 year old girl whose parents were first cousins. The child was small but well proportioned at birth; despite breast feeding until 17 months of age she developed slowly. At 2 years there were only 6 teeth; she did not walk until 3 years of age. Prolonged administration of irradiated ergosterol and phosphorus combined with exposure to sunlight failed to improve the rate of development.

At 4 years her bodily proportions were those appropriate to 1 year. Striking manifestations of rickets were present; the skull was not affected. The musculature was hypotonic.

Roentgen examination showed severe rickets, extreme osteoporosis and many pathologic fractures. Examination of the serum showed: calcium, 9.8 mg. per hundred cubic centimeters; inorganic phosphorus, 2.5 mg.; magnesium, 4.2 mg., and protein, 8.7 Gm. The carbon dioxide-combining power was 21.7 volumes per cent. The nonprotein nitrogen was 43 mg., the creatinine 1.5 mg., the uric acid 3.5 mg. and the cholesterol 184 mg. per hundred cubic centimeters.

The child excreted large amounts of urine, the volume varying between 800 and 1,000 cc. per twenty-four hours and the specific gravity between 1.023 and 1.032. Sugar was consistently present in concentrations of from 3 to 4, occasionally to 6, per cent; traces of acetone were often found in specimens collected before breakfast. Diacetic acid was never demonstrated.

The patient was treated intensively but ineffectively with ultraviolet rays, irradiated ergosterol and injections of phosphorus, with arsenic and by other means. An infection of the urinary tract set in and lasted intermittently for three months. Concomitant with this episode albuminuria and cylindruria made their appearance; red blood cells were never found in the urine. Incomplete tests of renal function failed to show impairment of the excretory capacity of the kidneys.

The fasting blood sugar varied between 80 and 88 mg. per hundred cubic centimeters. Dextrose tolerance tests were characterized by rapid ascent of the blood sugar to values between 185 and 197 mg. at sixty minutes followed by speedy descent to hypoglycemic levels after two and one-half hours; symptoms of hypoglycemia were often present with low concentration of blood sugar. The dextrose concentration of the blood was "little influenced" by injections of epinephrine hydrochloride; the response to insulin was similar to that of healthy subjects and was characterized by severe symptoms of hypoglycemia. The renal threshold for sugar was low; the urine continued to contain 4 to 5 per cent of sugar when the level in the blood was as low as 65 mg. per hundred cubic centimeters.

Treatment as outlined for a period of one year resulted in slight general improvement and some betterment of the roentgen features.

DEBRÉ, MARIE, CLÉRET AND MESSIMY, 1934.[38c]—The patient, a girl, was born at term; the birth weight was not recorded. She was breast fed until 13 months of age. Dentition commenced at 1 year, and the child started to walk at 14 months. She was regarded as healthy until 4 years of age, when a disturbance of gait was observed. Medical examination revealed the presence of rickets; the diagnosis was confirmed roentgenographically. Treatment with ultraviolet rays produced inconspicuous improvement. A trivial accident led to a pathologic fracture of the left femur; this healed in due time. Further treatment with calcium, vitamins, cod liver oil, fruit juices, salt water baths and exposure to sunlight was of little benefit. Arrest of growth in length became apparent during the eighth year of life. The intelligence was not affected.

A series of pathologic fractures led to more complete investigation. At 11 years the child was measured to be 102 cm. in length and was somewhat obese. The lower extremities were disproportionately short as the result of many fractures. Physical signs of severe rickets were present, but the skull was not affected. The liver was not enlarged. Roentgen examination revealed extreme osteoporosis involving all portions of the skeleton excepting the skull. The roentgen opacity of the bones was scarcely greater than that of the neighboring musculature; the epiphysiodiaphysial regions were thickened.

The urine was amber in color and cloudy, with a specific gravity of 1.031; it contained 0.22 per cent of albumin, a number of granular casts and leukocytes but no red blood cells. Sugar was present in concentration of about 1.5 per cent; both acetone and diacetic acid were detected. The excretion of organic acids was "much increased," and there was a substantial increase in the amount of mineral cationogens bound to these acids. (The data relating to these assertions are couched in unfamiliar and ambiguous terms; we cannot evaluate them critically. AUTHORS.) Maillard's coefficient (which we take to be the urinary ammonia coefficient) was 22, the normal range extending between 3 and 5. Although the

urinary p_H was not specified, the finding of a "diminished amount" of acid phosphate implies that the urine tended to be neutral rather than strongly acid. The authors also reported an increased concentration of organic acid and ammonia in the feces, the p_H of which was normal.

The urea content of the blood was 36 mg. The total protein content of the serum was 7.37 Gm. per hundred cubic centimeters, the albumin 4.84 Gm. and globulin 2.53 Gm.; the albumin globulin ratio was thus 1.9. The cholesterol content of the serum was 276 mg. per hundred cubic centimeters, and the total lipids amounted to 920 mg. The fasting blood sugar was 91 mg. per hundred cubic centimeters. Thirty minutes after the ingestion of 25 Gm. of dextrose the blood sugar rose to 200 mg. per hundred cubic centimeters, and after one hour, to 206 mg.; after one and one-half hours it fell to 160 mg.

The ingestion of 50 Gm. of dextrose led to an episode characterized by intense discomfort, extreme pallor and fainting, sunken eyes, cyanosis and tachycardia. Epinephrine restored consciousness temporarily, but the patient relapsed into coma accompanied by hyperpnea. The administration of sodium bicarbonate and small doses of insulin was fruitless; the child died during the test. The results of the only chemical analyses of the blood that were carried out at the time were as follows: fasting blood sugar, 159 mg. per hundred cubic centimeters; thirty minutes after the administration of dextrose, 385 mg. Necropsy was not permitted.

VAN CREVELD, 1934.[88d]—A 10 month old girl, the daughter of healthy parents, concerning whom no statement on consanguinity is recorded, entered the hospital because of progressive enlargement of the abdomen, which began at 5 months, together with fever, shortness of breath and increased thirst for a few weeks before her admission. She showed physical features of severe rickets, abdominal distention, enlargement of the liver to 5 cm. below the costal margin, moderate splenomegaly, masses in the flanks, thought to be due to polycystic kidneys, and bronchitis. The blood pressure was 90 mm. of mercury.

The volume of the urine was rather large and its specific gravity high. It contained much protein, was strongly reducing and gave a strongly positive reaction for acetone and a weak reaction for diacetic acid. Urobilin, urobilinogen and indican were also present in nonphysiologic amounts. The sediment contained many leukocytes. There was also anemia.

The blood sugar after a five hour fast was 83 mg. per hundred cubic centimeters. The serum calcium was 9.9 mg., the inorganic phosphorus 1.16 mg., the nonprotein nitrogen approximately 26 mg., the serum albumin 4.19 Gm. and the serum globulin 1.52 Gm. per hundred cubic centimeters. The serum cholesterol and the icterus index were normal. Roentgen examination revealed severe rickets.

The urinary reductant was shown to be a mixture of dextrose and glycuronates. The concentration of the former amounted to between 1 and 2 per cent; the latter was sufficient in amount to make the urine levorotatory. Elimination of foods and drugs which might be expected to increase the excretion of glycuronic acid did not produce its disappearance. A test of the sugar tolerance, involving the oral ingestion of 10 Gm. of dextrose, yielded the following values for sugar: fasting, 81 mg. per hundred cubic centimeters; after thirty minutes 117 mg.; after one hour, 114 mg.; after an hour and a half, 164 mg., and after two hours, 141 mg. Several days after admission the fasting sugar was 52 mg. per hundred cubic centimeters.

Treatment comprised the use of a mixed diet, insulin and small doses of extra sugar. Pyuria increased, but the amount of acetone in the urine and the degree of glycosuria diminished. Glycuronates almost disappeared. Nonetheless, the infant died with progressive dehydration.

Autopsy disclosed cirrhosis of the liver, with considerable fibrous tissue separating small islands of intact liver tissue; the periphery of these islands showed regeneration of the liver cells. The kidneys were large and firm; the pelves were dilated and the ureters enlarged, but there was no evidence of obstructive lesion. Chemical tests for amyloid and glycogen gave negative results. The endothelium of all the glomeruli, especially of those located most superficially, was of cuboidal conformation, reminiscent of the fetal type. The tubules were generally much dilated and their epithelium flattened. The supporting structures appeared normal.

The spleen, heart, pancreas and adrenals exhibited normal structure.

FORNARA, 1935.[44c,d]—Inasmuch as the patient was born out of wedlock, the details of the family history were not known; he weighed 2,450 Gm. when 10 days of age. A brief period at breast was followed by artificial feeding. Gain of weight was slow and unsatisfactory. The first tooth erupted at 10 months, and the infant began to walk at 15 months. At that time manifestations of severe rickets were evident in the thorax but not in the extremities; anemia with enlargement of the liver and spleen was detected. The urinary volume varied between 300 and 400 cc. daily, and the specific gravity between 1.015 and 1.025. The urine consistently contained a trace of albumin and at all times showed an amount of sugar varying from a trace to 2 per cent. Many white blood cells were present together with a moderate number of bladder epithelial cells and granular casts. The systolic blood pressure remained in the neighborhood of 90 mm. of mercury and the diastolic 70.

Fasting blood sugar values varied between 82 and 92 mg. Oral administration of dextrose was followed by a rapid rise to 155 mg. at fifty minutes and a prompt fall to values somewhat below the initial concentration at the end of two and a half hours. The serum nonprotein nitrogen was found to be between 31.5 and 37 mg. per hundred cubic centimeters on three occasions.

Treatment with various vitamin preparations, including irradiated ergosterol, produced definite benefit. Although albuminuria persisted, sugar disappeared from the urine and the amount of the urinary sediment became reduced. The state of nutrition improved. While this improvement was in progress, genu valgum developed. Roentgen films were described by Fornara as showing the epiphysial changes of rickets associated with oteoporosis; the published reproductions of the roentgenograms do not demonstrate these features clearly. Chemical examination of the blood showed the serum protein to be 7.17 Gm. per hundred cubic centimeters. The nonprotein nitrogen was 39 mg.; the calcium was "4.852" and the phosphorus "5.482" mg.

FLETCHER, 1934; [39b] HUNTER, 1935.[39a]—The patient, a 34 year old man, had become ill three years before with pain in the lower extremities. Physically, he manifested only painful limitation of motion of the hip joints and clubbed fingers. The blood pressure was normal. Roentgen examination showed generalized osteoporosis and several pathologic fractures. The urine contained sugar; other elements were not mentioned.

A test of the dextrose tolerance showed the glycuresis to be renal; the blood sugar curve was approximately normal. During a period of three and a half months the serum calcium varied between 9.8 and 11.9 mg. and the plasma inorganic phosphorus between 0.4 and 2.3 mg. per hundred cubic centimeters. The plasma phosphatase activity was slightly increased. On a low calcium–high phosphorus diet the patient manifested extreme hypercalciuria and hyperphosphaturia, with a negative balance for both elements.

Exploration of the neck failed to disclose a parathyroid adenoma; histologic examination of an excised parathyroid body yielded no evidence of hyperplasia. A fragment of the middle third of the right tibia was characterized by considerable osteoporosis but lacked features of osteitis fibrosa cystica and osteomalacia.

HUNTER, 1935.[39a]—As a child the patient had had rickets severe enough to require a brace. There was no history of dietary inadequacy or diarrhea. At 25 years pain in the hip led to a diagnosis of osteomalacia. This was treated ineffectively with epinephrine, "prolan," "pituitary extract," irradiated ergosterol and calcium lactate.

At 29 years the patient was fairly well nourished but moderately deformed, with severe genu valgum and scoliosis. The blood pressure was not elevated. Roentgenograms revealed severe osteoporosis, much bony deformity and several pathologic fractures.

The urine was acid and contained albumin, sugar and a few leukocytes but no casts. The excretion of phenolsulfonphthalein was much reduced, and the standard urea clearance test showed a renal function of less than 50 per cent of normal. The fasting blood sugar was 57 mg. A dextrose tolerance test yielded a normal curve; there was persistent glycosuria throughout the test.

During a period of five weeks the serum calcium content varied between 9.5 and 11.6 mg. and the plasma inorganic phosphorus between 1.0 and 2.8 mg. per hundred cubic centimeters; the plasma phosphatase activity was approximately normal. A low intake of calcium resulted in a negative balance characterized by hypercalciuria.

Treatment for over a year with a high calcium diet, medicinal calcium and vitamin D produced no improvement. The serum calcium, and the plasma inorganic phosphorus and phosphatase activity showed no significant change. Surgical exploration of the neck and the mediastinum failed to disclose a parathyroid adenoma. One of the glands was removed and shown microscopically to possess normal structure. The presence of a great excess of osteoid tissue and imperfectly calcified bone in a specimen of bone removed from the tibia led to a diagnosis of osteoporosis and osteomalacia.

BENOIT, 1935.[48]—Of the medical history all that is recorded is that the patient was a 3¼ year old boy who had florid rickets and tetany. He was 72 cm. in length and weighed 6.6 Kg.

Autopsy confirmed the rachitic nature of the skeletal disease and showed that it was of severe degree. The parathyroid glands were enlarged but of normal cellular structure. The kidneys showed pyelonephritic scars, and hemorrhagic cystitis was present. Enclosed within phagocyte cells throughout the interstitial tissue of the spleen, liver, thyroid, pancreas, adrenals, lungs, kidneys, lymph nodes and bone marrow were large numbers of translucent polygonal crystals. The accumulation was most dense in the lymph nodes. There were occasional foci of parenchymatous necrosis in the liver. In the kidneys, aside from the "pyelonephritic changes," there was conspicuous proliferation of the glomerular endothelium. Neither atrophy nor hypertrophy of the tubular epithelium was described. The crystals were thought to be composed of calcium. They lacked double refractility, were turned black by the von Kossa technic, were converted into "gypsum" on the addition of sulfuric acid and gave off "bubbles of carbon dioxide gas" when hydrochloric acid was applied.

Roulet [48b] convincingly disputed Benoit's identification of the chemical nature of the deposited substance and provided acceptable evidence that it was cystine: 1. Benoit's description of the translucency of the crystals, their refusal to accept the

hematoxylin stain, their lack of double refractility and their rapid disappearance from tissues preserved in commercial solution of formaldehyde exactly characterized the deposited material in Roulet's case; this was proved to be cystine. 2. Cystine which is deposited in tissues also gives a positive von Kossa reaction (Roulet's own observation) by virtue of the adsorption of reduced silver on the cystine crystals. The reduction is brought about by the action of cysteine, which, on the basis of considerations of redox equilibrium, must be assumed to be present whenever crystalline cystine is encountered in the body. Cysteine reduces silver nitrate promptly. 3. Calcium does not appear in tissues in visibly crystalline form but occurs as an amorphous precipitate. The crystals which were described and illustrated by Benoit were identical with those which have been found in the tissues of persons known to have cystinosis.

FANCONI, 1936.[13b,c]—*Case 1.*—The patient, a girl, was born of elderly, nonconsanguineous parents and weighed 3,350 Gm. Rickets was recognized at 3 months. Irradiated ergosterol was given, and the infant developed well until she was 6 months of age, when she lost appetite, vomited daily and sweated a great deal. Urinalysis at 1 year of age revealed albumin, numerous leukocytes, many granular casts and colon bacilli. Shortly thereafter sugar made its appearance, varying in concentration from 0.5 to 2.5 per cent. The fasting blood sugar fluctuated widely, between 56 and 160 mg. per hundred cubic centimeters; the largest number of values were under 100 mg. The nonprotein nitrogen was slightly increased, varying between 29 and 61 mg. per hundred cubic centimeters. Roentgen examination at 1 year showed osteoporosis without rickets. During the second year of life osteoporosis increased and rickets became manifest. Treatment with irradiated ergosterol, cod liver oil and a diet containing a large excess of mineral cationogens initiated healing of the rickets and slight acceleration of the rate of growth.

During a twenty months' stay in the hospital between the ages 12 and 32 months the child grew only 7.5 cm. There were persistent glycosuria, albuminuria and cylindruria, as well as unexplained wide daily fluctuations of body temperature from subnormal values, of 35 C. (95 F.) to febrile levels of 38 C. (100.4 F.).

During the fourth year of life the situation improved, with disappearance of sugar from the urine; albumin persisted.

Near her fourth birthday the child suffered an attack of jaundice; nine months later she had difficulty in walking and became bedridden. A single episode of what appeared to be tetanic spasm occurred; the serum calcium and phosphorus levels were not determined. When last submitted to investigation, at 5½ years, she was approximately 14 per cent below her expected height and seriously undernourished. The urine contained 2 per cent of protein, no sugar, and large numbers of casts but no leukocytes or red blood cells. The nonprotein nitrogen content of the blood was 83 mg. and the sugar content 126 mg. per hundred cubic centimeters. The systolic blood pressure was 87 mm. and the diastolic 70. In twenty-four hours she voided only 130 cc. of urine; this had a specific gravity of 1.007. Roentgenograms showed extensive osteoporosis, conspicuous widening of the rachitic intermediary zone and a honeycomb rarefaction of the spongy portions of the long bones. Only four centers of ossification were present in the carpus. After an attack of clonic convulsions of unidentified cause, the patient died suddenly, aged 5 years 6 months.

The necropsy was described in full detail by Sturzenegger.[13d] Histologic examination of the skeleton revealed severe rickets with: (*a*) increase in the width of the zone of proliferating cartilage; (*b*) incomplete, interrupted or absent zone of preparatory calcification; (*c*) invasion of the proliferating cartilage by the marrow vessels, with

destruction of the cartilage or its conversion into osteoid, and (*d*) widespread appearance of osteoid in moderate amount at the margins of all periosteal and endosteal surfaces as well as in the haversian canals. Resorption of bone predominated conspicuously over its production. There was a pronounced increase of the fibroblastic elements of the marrow. A feature of especial interest was the occurrence of dissection of the secondary spongiosa and of the compacta by marrow radicals composed of fibrous tissue. The foregoing features were demonstrated throughout the skeleton; the skull alone appears to have been unaffected.

In the kidneys the glomeruli were normal in size and number. The capillary tufts and the capsular lining appeared to be of normal delicacy; in only a few places was there evidence of thickening of the capsular membrane. Severe alterations were present in the renal tubules. The convoluted tubules were widened, in some places to the point of being almost cystic. The tubular epithelium was partly flattened to the dimensions of endothelium and partly swollen, with obliteration of the intercellular margins. The cells gave the appearance of having been packed with a substance soluble in either alcohol or water, so that the process of fixation left recognizable only a network of protoplasm within the cells. Sturzenegger suspected that the soluble material might have been cystine but lacked differently preserved material for analysis. There were a few small inclusions of lipoid material. The features of distinction between the proximal and distal tubules were obliterated, with the result that the vacuolated epithelium resembled that proper to the proximal tubules. The lumens were filled with droplets of urine, cellular detritus and granular casts. The changes in the epithelium of the loops of Henle were similar to those in the convoluted tubules. The renal vessels were normal. The interstitial substance contained a few patches of lymphocytic infiltration. There were no gross anomalies of the urinary tract.

The thyroid and parathyroid glands and the pancreas were normal. Significant changes were not encountered in the adrenal glands, the heart muscle or the spleen. The liver cells also appeared normal. The lungs showed only edema.

Case 2.—The parents of Fanconi's second patient were elderly first cousins. The patient, a girl, weighed only 2.5 Kg. when born, at term. She was fed at breast for fourteen weeks and then with formulas of diluted cow's milk. Development progressed satisfactorily during the first six months of life; after an attack of otitis media retardation became evident. She did not sit up until she was 10 months of age, and the first tooth was not erupted until 14 months. Albuminuria was detected at 11 months; at that time the urinary sediment was normal.

At 15 months of age the child was studied in the Children's Hospital, Zurich, Switzerland, where she died six weeks after admission.

The stature was about 16 per cent below normal and the weight approximately 30 per cent below that expected in relation to height. Rickets was evident. The liver was felt 2 fingerbreadths below the costal margin; the spleen was not palpable.

Roentgen examination revealed active rickets and osteoporosis. The serum calcium was 9.6 mg. and the serum inorganic phosphorus 2.2 mg. per hundred cubic centimeters. The nonprotein nitrogen was 35 mg. per hundred cubic centimeters and the serum chloride 106 milliequivalents per liter.[52a] The total protein was 8.32 Gm. per hundred cubic centimeters, and the albumin globulin ratio was approximately 2.

52a. The original gives 621 mg. per hundred cubic centimeters. This equals 106 milliequivalents per liter ($\frac{621 \times 10}{58.45}$). Similar calculated values derived from figures given in the original reports occur in some of the succeeding cases.

As indicated by the insolubility of the sediment, the urine contained an increased amount of phosphorus. There were a faint trace of albumin and 3.6 per cent of sugar but no acetone or diacetic acid; the sediment contained crystals and a few red blood cells.

The spinal fluid was normal. Hematologic examination yielded unimportant results.

The fasting blood sugar level varied between 68 and 161 mg. Dextrose tolerance studies demonstrated a sharp rise of the blood sugar from fasting values of from 100 to 150 mg. to hyperglycemic levels, of more than 300 mg. per hundred cubic centimeters. Both times that dextrose was administered for test purposes, the child became severely ill.

During the six weeks before death the patient had irregular elevations of temperature, up 40 C. (104 F.). Albuminuria and glycosuria persisted; granular casts and many leukocytes made their appearance in the sediment. The child died at 16 months of age during the course of a febrile episode characterized by convulsions.

The important observations at autopsy were malnutrition, extensive fatty infiltration of the liver and some degree of fatty infiltration of the basal stratum of the proximal convoluted tubules. The pancreas was normal. The midbrain was examined with especial care and was also found to be normal.

Case 3.—Fanconi's third patient was a girl. Although not proved, parental consanguinity was strongly suspected. An investigation of the ancestry revealed several cases of renal disease in preceding generations. In addition, the child's oldest brother had died of what was thought to be renal rickets.

The patient weighed 2,500 Gm. at birth; she was nursed at breast for three weeks and then given a regular diet, which she took poorly. Her first tooth erupted at 5 months. Rachitic enlargement of the wrists and knees became evident at 15 months. Cod liver oil and calcium were given without apparent benefit.

At 18 months the child was admitted to a hospital, where she remained for more than a year; during this period extensive studies were made.

The pathologic physical conditions consisted in underdevelopment, undernutrition and conspicuous evidence of rickets. Roentgen examination showed florid rickets and osteoporosis. Vigorous therapeutic measures produced slight calcification of the skeleton but were without permanent benefit to the patient. The course in the hospital was characterized by recurrent bouts of unexplained fever.

Chemical examination of the blood showed variation of the calcium content of the serum from 7.7 to 11.6 mg. per hundred cubic centimeters; the inorganic phosphorus content fluctuated between 1 and 3 mg. per hundred cubic centimeters. The phosphatase activity was 14.2 Bodansky units. The nonprotein nitrogen was elevated to 40 mg. on one occasion but was found to be normal at all other times. A single determination of the carbon dioxide–combining power of the serum, on a day when the urine was alkaline to litmus, gave a value of 31.9 volumes per cent. The concentration of chlorides remained at approximately 100 milliequivalents per liter; the total protein varied between 7.9 and 8.8 Gm. per hundred cubic centimeters with an albumin globulin ratio of approximately 2.5. The fasting blood sugar ranged between 77 and 138 mg. per hundred cubic centimeters. Tests of the dextrose tolerance yielded somewhat variable results: There was extreme hyperglycemia followed by delayed return of the blood sugar to normal values. The patient suffered considerable discomfort during the tolerance tests.

Nearly every urinalysis demonstrated albumin. Glycosuria was present during the early months of the hospital study, the concentration of sugar varying from

0.4 to 0.8 per cent. The urinary sugar diminished during the last few months before death and occasionally disappeared entirely. The modal urinary p_H was 7.14; the lowest, 6.99. The specific gravity showed a range of from 1.005 to 1.020. The sediment contained epithelial cells and leukocytes, occasionally erythrocytes and a varying number of granular casts.

On the basis of the melting point of the osazone crystals the reducing substance in the urine was shown to be largely dextrose; some levulose was also demonstrated. Whether or not this was due to inversion of dextrose in the alkaline urine was not determined.

Equivocal evidence was obtained to indicate a diminished capacity of the kidney to excrete highly concentrated and extremely dilute urine.

The excretion of organic acids by the kidneys was shown to be increased by about three to five times the normal amount. Since repeated tests failed to demonstrate the presence of either acetone or diacetic acid and since Millon's test showed tyrosine to be present, it was suspected that the hyperaciduria was due to amino acids.

RUSSELL AND BARRIE, 1936.[41]—*Case 1.*—The patient, a girl, was born normally at term, weighing 4.5 Kg. Rickets was evident at 14 months; at that time albumin and sugar were found in the urine. The urea nitrogen content of the blood was 18 mg. A dextrose tolerance test yielded a normal curve. At 11 years she was underdeveloped and deformed. There was slight hypertension. The liver and spleen were not felt. Roentgen examination revealed the fluffy type of rickets. The urine was acid and contained albumin, many hyaline and granular casts, a few erythrocytes and sugar, even at times when the blood sugar was in the neighborhood of 100 mg. per hundred cubic centimeters. Although the urea nitrogen content of the blood was only 15 mg. per hundred cubic centimeters, the standard urea clearance test showed reduction to one-quarter normal. The calcium content of the serum was about 10 mg. and the inorganic phosphorus content approximately 3 mg. per hundred cubic centimeters. The plasma phosphatase activity was increased. With a known low calcium intake the excretion of calcium in urine and feces was regarded as normal. Routine antirachitic treatment was without benefit.

Eighteen months later arterial and intracranial hypertension developed and the child died; the urea nitrogen had remained unchanged. Autopsy disclosed widespread storage of cystine crystals throughout the reticuloendothelial system, severe rickets and advanced Bright's disease.

Since cystine had never been detected in the urine during life, the denouement was entirely unsuspected. Although further inquiry failed to reveal a familial cystinuric diathesis, it was learned that a sibling had died at 5 years of an apparently like disorder.

Case 2.—The patient, a 16 year old boy, was treated for rickets from 18 months to 7 years of age. He had "always" passed a large volume of urine. His fatal illness was characterized by vomiting, diarrhea and shortness of breath, terminating in tetany, anuria, delirium and coma. The systolic blood pressure was 210 mm. of mercury and the diastolic 110. The urine contained much albumin but no sugar or acetone. The urea nitrogen content of the cerebrospinal fluid was approximately 120 mg. and the calcium content 4.6 mg. per hundred cubic centimeters.

Autopsy disclosed deposits of cystine crystals distributed much as in the first case; the number of crystals was smaller. The changes in the kidneys included virtually complete destruction of glomeruli. Atrophy of the tubules was impressive and regeneration scanty. There was diffuse homogeneous fibrosis of the supporting structures. The bones were not examined. The authors expressed the inference that conspicuous deformity of the skeleton was absent.

BEUMER AND WEPPLER, 1937.[45f]—The patient, a boy, was the only child of healthy parents. He weighed 3.7 Kg. at birth. Discounting moderate pallor, he was found to be well nourished and healthy when examined at 2 months of age. He was fed at breast and did well until an attack of measles at 9 months. His appetite waned, and he became marantic, weighing at 10 months 200 Gm. less than at 2 months; growth in length also became slow. Signs of moderate rickets were apparent; the liver extended 2 fingerbreadths and the spleen 1 fingerbreadth below the costal margin. The systolic blood pressure was 105 mm. of mercury and the diastolic 80. The urine contained albumin (1 plus), a few leukocytes and casts and sugar. During four months' observation unyielding anorexia persisted and bouts of unexplained fever occurred. The use of insulin was fruitless. After an interval of rapid loss of weight uremic breathing set in and death followed.

Throughout the period of observation protein up to 1 Gm. per liter and 1 to 2 per cent of sugar appeared consistently in the urine. A moderate number of casts and leukocytes as well as occasional erythrocytes were observed in the sediment. Acetone was not detected. The urinary sugar was identified as dextrose. No crystals of any kind were observed.

The glycosuria was shown to be renal; the fasting blood sugar fluctuated between 96 and 135 mg. The oral ingestion of 20 Gm. of dextrose led to rapid rise to 197 mg. after thirty minutes, with return to 81 mg. at the end of two hours. The serum nonprotein nitrogen varied between 26 and 31 mg. per hundred cubic centimeters, rising to 98 mg. eight days before death. Glycosuria disappeared just before the boy's death.

Autopsy revealed the megascopically visible presence of cystine crystals in the interstitial tissues of the liver, spleen, kidneys and thymus. In the kidneys these were distributed focally along the blood vessels and about the glomeruli. The glomeruli, although underdeveloped, were relatively well preserved. The most conspicuous alterations were proliferation of the interstitial supporting tissues and atrophy of the tubules; some of the latter were much dilated and contained colloid debris. Surrounding the cystine deposits in the liver there was some cellular degeneration. Crystals were most numerous in the spleen, where they involved the arterioles and the follicles, with production of considerable connective tissue; in this organ there was some phagocytosis of crystals.

GUILD, PIERCE AND LILIENTHAL, 1937.[38e,f]—Gould described briefly the case of a 17 month old girl, the child of nonconsanguineous parents, who had had feeding troubles from early infancy and who had developed poorly. She showed signs of rickets early in life; the disease progressed in spite of usual treatment. Increased frequency of urination had "always been present," and at 6 months "renal glycosuria was discovered." Thirst and polyuria were noted later. Frequent episodes of unexplained fever appeared. The infant gained no weight after the tenth month of life and manifested pain on being handled from 15 months onward.

When brought to the Harriet Lane Home at 17 months of age, she was undernourished, showed signs of florid rickets and manifested defective dentition. The abdomen was distended; the liver was large and hard with an irregular margin, and the spleen was palpable.

During the period of investigation the calcium content of the serum approximated 8 mg. and the inorganic phosphorus content 1.3 mg. per hundred cubic centimeters; there was "a slight increase in chlorides and a content of total fixed base within normal limits." An unsatisfactory determination showed "a suggestively significant increase in the total organic acid content" of the serum. The vitamin D content

of the serum was found to be within normal limits.[50b] The Hamilton test [53] failed to reveal an increased concentration of parathyroid hormone in the blood. The serum phosphatase activity was 49.9 Bodansky units. A metabolism study showed a negative balance for calcium and phosphorus.

The volume of urine was increased. The p_H averaged 6.5, being relatively high in relation to the degree of acidosis. Albuminuria was present, with a few casts and white blood cells. Glycosuria was conspicuous and consistent; traces of acetone were occasionally present. The glycosuria was shown to be of renal origin; the threshold was under 65 mg. per hundred cubic centimeters. Twenty to 30 Gm. of sugar appeared in the urine daily. Tests of the dextrose tolerance showed a rapid rise of the blood sugar from a fasting value of 60 to 180 mg. at the end of one hour, followed by a sharp fall to 50 mg. at the end of two hours.

The nonprotein nitrogen content of the blood was 30 mg. per hundred cubic centimeters, and the excretion of phenolsulfonphthalein was 50 per cent in two hours. It was demonstrated that the kidneys could concentrate to a specific gravity of 1.015, corrected for the sugar content of the urine.

Approximately twenty times the normal amount of organic acid was excreted in the urine each day. The ammonia content of the urine was greatly increased, and the phosphorus content was relatively high.

Unsuccessful attempts were made to combat the acidosis with sodium bicarbonate and sodium lactate; drowsiness and distention ensued. The administration of large amounts of vitamin D raised the serum inorganic phosphorus slightly and caused some healing of rickets as judged by roentgen evidence. Death took place from intercurrent infection.

Autopsy revealed cirrhosis of the liver. In addition, the epithelial cells of the renal tubules showed peculiar enlargement, sometimes to the point of almost blocking the lumen. Tubular degeneration, in the ordinary sense of the word, was lacking.

PINCUS, 1937.[38g]—In the discussion which followed the presentation of Guild's case Pincus spoke of a similar case the details of which were published with Gettleman in 1940.[38]

SMYTH, 1937.[38l]—In the same discussion Smyth mentioned an additional case, involving a 5 year old child. The serum bicarbonate level was low, and there was slight albuminuria. Administration of 50,000 U. S. P. units of vitamin D daily produced favorable results. The serum inorganic phosphorus rose from 1.5 to 5 mg. per hundred cubic centimeters during a fourteen month period of observation.

NOBÉCOURT, CATHALA, BRISKAS AND MOREL, 1938.[38l]—The patient, a girl, was the third child of nonconsanguineous parents. Her weight was average when born at term. Breast feeding was practiced for three weeks; then evaporated milk, malted cereal and fruit juices were given. The appetite was poor from the beginning. At 6 weeks of age unexplained fever made its appearance; the liver was noted to be enlarged at that time. The first tooth erupted at 5 months; the child was able to stand erect at 18 months and commenced to walk two months later. At 2 years manifestations of severe rickets were evident; henceforth she grew poorly, had an extremely unsatisfactory appetite and was severely constipated. By 3 years of age the rachitic deformities were so incapacitating that a plaster cast was required.

The studies on which the report was based were made when the child was 4 years of age. She was then moderately dwarfed and seriously undernourished

53. Hamilton, B., and Highman, W. J., Jr.: A Test for Abnormally Large Amounts of Parathyroid Hormone in the Blood, J. Clin. Investigation **15**:99 (Jan.) 1936.

and exhibited extensive rickety deformities of the skeleton, with severe muscular hypotonia. The abdomen was hugely distended, the liver large and hard. The systolic blood pressure was 106 mm. of mercury. The Mantoux and Wassermann reactions were negative.

Roentgen examination revealed active rickets of great severity associated with osteoporosis. The skull was not affected so severely as other parts of the skeleton; there were no pathologic fractures.

Chemical examination of the blood, repeated frequently during a period of four months, revealed a concentration of urea of approximately 40 mg. per hundred cubic centimeters; serum calcium, 8.8 to 9.8 mg., and serum inorganic phosphorus, 1.5 to 1.9 mg. The total phosphorus was also reduced. The cholesterol was 250 mg., the total lipids 950 mg. and the total protein 8.6 Gm. per hundred cubic centimeters.

Polyuria was not observed. The urine contained consistently about 0.5 Gm. of albumin per liter and from a trace to 0.68 per cent of sugar. Traces of acetone were also present. At no time were casts or red blood cells found; occasionally epithelial cells and a few white blood cells were encountered. The excretion of phenolsulfonphthalein was found to be 55 per cent and 43 per cent within two hours on successive tests.

The fasting blood sugar varied between 73 and 150 mg. per hundred cubic centimeters. Two dextrose tolerance tests showed a moderate increase of blood sugar, amounting to about 100 mg., over the fasting level at the end of sixty to ninety minutes. Both tests showed prolongation of the time required for the concentration of sugar to return to normal. Hypoglycemia was not observed.

During her stay in the hospital the child exhibited pronounced lability of body temperature. Treatment with an abundant and varied diet, vitamin D concentrates and two months of daily injections of an extract of the anterior lobe of the hypophysis failed to produce any improvement.

Rössle, 1938.[49c]—The patient was a 4 year old girl. The father was a victim of active tuberculosis; the mother had heart disease and gout; a brother was under medical supervision because of tuberculosis. At about 2 years of age she commenced to manifest progressive loss of appetite and weakness, associated with increasing thirst; this culminated in a daily intake of fluid amounting to 3 to 4 liters. She was studied in the hospital for only a few days before death. Her length was 89 cm., approximately 9 cm. below the average. The heart and lungs were normal; the liver and spleen were not enlarged. The Wassermann test of the blood as well as the Pirquet and Mantoux tests gave negative results. The urine contained a trace of albumin and a slight increase in the concentration of urobilinogen. The specific gravity was 1.005. There was neither sugar nor ketones; the diazo reaction was negative. The roentgen features of the skull were normal. Death was ushered in by irritability, restlessness, vomiting and coma.

Postmortem examination disclosed widespread deposits of doubly refractile rhombic crystals in the kidneys, liver, spleen, bone marrow and lymph nodes, particularly those of the mesentery. The kidneys weighed about one third of normal. The glomeruli appeared intact. The tubular epithelium was partly atrophic or necrotic, partly hypertrophic. Deposit of crystals was confined to the interstitial tissues of the affected organs. Although the architecture of the liver was normal to the naked eye, the microscope revealed a pattern of destruction of some cells combined with swelling of others, not dissimilar to that presented by the kidneys. In these organs as well as in the liver and most conspicuously in the spleen and lymph nodes the crystals were enclosed within large phagocytes and were nowhere found inside the parenchymatous cells themselves.

The microscopic features of the cartilage-shaft junction were not described. However, the statement that this region was grossly normal in the ribs permits the inference that rickets was not present. Although the left inferior parathyroid body was enlarged, the cellular structure was normal.

On finding the deposits in paraffin sections, Rössle sought to determine their chemical nature; in the meantime the crystals had disappeared from the surplus material which had been preserved in solution of formaldehyde, leaving behind only rod-shaped lacunas and the cellular alteration due to their previous presence.

Circumstantial evidence tends to confirm Roulet's [43b] suggestion that the crystals were composed of cystine. Strong support of this opinion is drawn from the similarity of the microscopic features of the lymph nodes in the 2 cases. (Compare Rössle's figure 2 with Roulet's figure 13.)

GOLDMANN AND EKSTEIN, 1939.[38k]—This case was studied in Czechoslovakia. The patient, whose sex was not stated, was the first-born child of nonconsanguineous parents. The birth weight was 3,850 Gm. The infant was weaned at 8 months. The first tooth appeared at 6 months, and the child began to walk at 10 months. When rickets became manifest was not stated, but the child stopped walking at 18 months because of weakness. Large doses of cod liver oil, vitamin D concentrates, calcium and ultraviolet rays failed to arrest the progress of rickets.

At 2 years the weight was 8,700 Gm. and the height 75 cm. The skeletal features of rickets were conspicuous and pronounced muscular hypotonia was present. The systolic blood pressure was 80 mm.

Roentgen examination revealed severe active rickets, extreme osteoporosis and numerous pathologic fractures. The maturity of the skeleton corresponded to that of a 1 year old child. The calcium content of the serum was 14 mg. and the inorganic phosphorus 1.4 mg. The fasting blood sugar varied between 50 and 65 mg. The nonprotein nitrogen content of the whole blood was 32 mg. per hundred cubic centimeters.

The daily output of urine was small, averaging about 100 cc.; the specific gravity, apparently not corrected for sugar content, was 1.030. Albumin was occasionally present. The urine was consistently alkaline; it contained sugar in concentration of about 2 per cent. The sediment showed a few granular casts. The presence of tyrosine was demonstrated by a qualitative test. The concentrating and diluting powers of the kidney were normal. The child excreted large amounts of organic acid in the urine. The types were not identified.

A metabolism study revealed a negative balance for nitrogen and phosphate and a positive balance for calcium, sodium, chlorine and potassium. The loss of phosphorus was conspicuous; it occurred largely through the feces. Treatment with a massive single dose of vitamin D produced no benefit. The use of a diet containing an excess of mineral cationogens, in which potassium predominated, is said to have effected dramatic improvement: The retention of phosphorus assumed normal proportions, and the balance of cationogens was also improved. The inorganic phosphorus content of the serum increased from 1.4 to 2.1 mg. and the calcium content from 14.1 to 17.59 mg. per hundred cubic centimeters (!). Glycosuria disappeared.

Many of the biochemical data contained in the report are so ambiguously recorded and others so open to question of technical reliability that their interpretation is highly insecure.

CAUSSADE, VERAIN AND NEIMANN, 1940.[44e]—As one of 3 examples of arrest of growth due at least in part to disturbance of renal function, the authors described the case of a 6½ year old boy. Consanguinity was not mentioned. The child was

born at term; the weight was not known. He was fed at breast. The first tooth erupted at 7 months; he walked at 10 months and talked at 15 months. At 15 months bilateral genu valgum became evident. Osteotomy was not permanently successful in correcting deformity. This increased progressively despite a diet which was described as unexceptionable, combined with medicinal calcium and vitamin D in doses which were not specified.

At 6½ years the boy was dwarfed, his stature being that of a 2 year old; nutrition was not seriously compromised. Superficial manifestations of severe rickets were present; the lower extremities were more severely affected than the upper. The skull was not involved, and a rickety rosary was lacking. The muscles exhibited extreme hypotonia. Roentgen examination confirmed the diagnosis of active rickets and showed, in addition, the presence of nine pathologic fractures and retardation of development of the carpus to the 2½ year level.

The volume of the urine was increased to between 800 and 1,200 cc. daily. Albuminuria amounted to between 0.1 and 0.25 per cent. The urinary sediment contained many polymorphonuclear leukocytes, a few renal epithelial cells and hyaline casts, together with occasional erythrocytes. The urinary content of urea was approximately 0.9 Gm., of calcium 0.13 Gm. and of phosphorus 0.16 Gm. per hundred cubic centimeters. There were traces of sugar but no ketone bodies. The concentrating and diluting capacity of the kidneys was reduced. A phenolsulfonphthalein test showed the excretion of 40 per cent of the dye in seventy minutes. Ambard's coefficient was increased to 102. The carbon dioxide–combining power of the serum was 49.7 volumes per cent. The serum chloride was 126 milliequivalents per liter, with a normal ratio of 0.55 between erythrocyte and plasma chloride. The cholesterol content was 162 mg. The calcium content of the serum was 10.5 mg. per hundred cubic centimeters; the inorganic phosphorus content was not reported. The phosphatase was normal. The p_H of the blood was 7.52.

Studies of the blood sugar were not made; the excretion of organic acids was not determined. It does not appear that aggressive treatment was attempted. In any event, at the end of a year's observation the boy's general condition was unchanged.

GITTLEMAN AND PINCUS, 1940.[38h]—The patient, a girl, was born at term, weighing 3.7 Kg. The parents were not related by blood. A sister had died of rickets and pneumonia. The child developed slowly, had frequent colds and a poor appetite. She suffered an attack of severe pertussis at 1 year. Physical examination at 2 years showed the liver to be 1½ fingerbreadths below the costal margin but revealed no superficial evidence of rickets. At 3½ years the gait became insecure, and finally the child refused to walk. After seeking assistance in several clinics, where she was treated fruitlessly with large doses of vitamin D, the child was brought to the attention of the authors.

At that time she was 4½ years old, was 94 cm. in length and weighed 14 Kg. Deformities of rickets were manifest together with slight enlargement of the liver and spleen. The systolic blood pressure was approximately 110 mm. of mercury and the diastolic 80. Roentgen examination confirmed the activity of the rickets.

The urine was acid, had a specific gravity between 1.012 and 1.028 and contained albumin (up to 2 plus), granular and hyaline casts and varying amounts of acetone. Sugar was persistently present in concentrations up to 0.4 per cent. The reducing substance was described as having been composed of nearly equal parts of dextrose and fructose. The method of identification was not given, and the amount excreted in twenty-four hours was not specified. When phenolsulfon-

phthalein was injected intramuscularly it was excreted to the extent of 79 per cent in two hours; when it was injected intravenously, 65 per cent was excreted in the same time. An intravenous urogram yielded normal results.

The calcium content of the serum was 10.8 mg. per hundred cubic centimeters, the inorganic phosphorus content 2 mg. and the cholesterol content 276 mg; the phosphatase activity was 32 Bodansky units, and the chlorine content was 105 milliequivalents per liter. The carbon dioxide-combining power of the blood was 36 volumes per cent.

Extensive investigations of the mineral metabolism were carried out over a period of five months. While receiving a diet of average composition, the child was found to be in negative balance for calcium and phosphorus. The addition of 6,250 U. S. P. units of vitamin D (in the form of D_2 in propylene glycol) daily increased the net absorption of calcium and phosphorus, reduced their excretion by the kidneys and produced a retention of both minerals. The positive balance of phosphorus developed more slowly than that of calcium. The retention was small, and the inorganic phosphorus level of the serum remained low. Addition of 15 millimols of orthophosphoric acid daily supplemented these effects, so that for a short time the retention ratio of calcium to phosphorus reached 2 and the serum inorganic phosphorus level rose briefly to 2.6 mg.; some improvement of calcification was evident in the roentgenograms. The benefit of the combined treatment was of short duration: After a few weeks the retention of phosphorus diminished, the concentration declined to its previous level and further calcification of the rachitic metaphysis failed to materialize. It is of considerable interest that hyperphosphaturia persisted virtually unaltered throughout the entire study. At the beginning, the excretion of phosphorus in the urine amounted to over 100 per cent of the net absorbed phosphorus; with increasing absorption 80 per cent continued to appear in the urine despite low concentration in the serum and in the presence of a defectively mineralized skeleton. The substitution of approximately 80 millimols of dicalcium phosphate, first alone, then combined with vitamin D, for phosphoric acid was not followed by clinical improvement, despite the fact that the retention of phosphorus was somewhat improved and the amount of the net absorbed phosphorus which appeared in the urine fell to 65 per cent. Subsequently, the administration of disodium phosphate in doses approximating 35 millimols daily for a period of more than two months appeared to be fruitless; increased osteoporosis was noted. It was not stated whether or not vitamin D was employed during this period.

Simultaneous studies of the balance of sodium, potassium, magnesium, chlorine and nitrogen failed to supply informative results.

Reduction of serum bicarbonate was ascribed to ketosis. This explanation was based on the fact that, whereas the blood lactic acid was normal, the blood ketones were increased; with disappearance of ketosis under the influence of lipocaic the serum bicarbonate rose toward normal concentration. However, when ketosis was abolished with insulin the bicarbonate was not affected.

The nature of the glycosuria was not clearly defined. It was not modified by insulin. The fasting blood sugar varied between 70 and 120 mg. per hundred cubic centimeters. The response to the oral ingestion of test doses of dextrose was characterized, except in one instance, by a somewhat less than average rise, which, however, was prolonged below average expectation. Although it was not stated specifically, we infer that glycosuria was present during the tests despite the fact that in only two instances did the blood sugar exceed the usual threshold level, of 160 to 180 mg. per hundred cubic centimeters. Because of the favorable response

to lipocaic, which included slight reduction of the size of the liver, there was assumed "a disturbance in the internal secretion of the pancreas, in some way analogous to that found in diabetes mellitus but different from it in many important essentials." It appears warranted to suspect that the glycosuria was renal.

Additional observations were a higher level of vitamin D in the blood than in that of a comparable normal control subject; no increase of the parathyroid hormone in the blood as determined by the technic of Hamilton and Schwartz, and a normal rate of basal metabolism. Numerous data on the anion-cation balance in the blood are reported. For these and other items of information the reader is referred to the original.

The authors implied the opinion that the primary lesion was located within the pituitary gland and was associated with a disturbance of the function of the pancreas. The manifestations of disordered renal function were thought to be of secondary consequence.

PACHE, 1940.[46]—Pache's patients were a brother and sister. The paternal grandfather gave a history of kidney stones, and one of the mother's aunts had curvature of the spine, which was thought to be the sequel of severe rickets.

The sister was born normally at term. She weighed 3.3 Kg. at 6 weeks of age and developed normally in all respects until the age of 8 months, when a febrile illness with vomiting made its appearance. At 11 months she weighed 7.2 Kg. and was 71.5 cm. in length. The state of nutrition was fair. At that time the urine was found to contain albumin, white blood cells and hyaline casts. Acetone was present for a few days. The nonprotein nitrogen content of the blood was 30.2 mg. per hundred cubic centimeters. A retrograde urogram revealed a morphologically normal urinary tract. The roentgen aspects of the skeleton included some degree of retardation of carpal ossification and signs of atrophic rickets. The serum phosphate was 2.97 mg.; the calcium was not determined.

Repeated vomiting made its appearance, and the child gained poorly, weighing only 6.7 Kg. at 18 months. The urinary sediment showed no improvement and occasionally contained erythrocytes. The nonprotein nitrogen remained normal. Intensive treatment with irradiated ergosterol combined with sunlight produced unmistakable evidence of healing of rickets. The serum inorganic phosphorus rose to 3.88 mg.; again the calcium was not measured.

The child started to walk at 2¼ years. At that time Freudenberg and Bersin isolated cystine from the urine. At about the same time conspicuous polydipsia appeared; this symptom was not relieved by the use of "hypophysis preparations."

Difficulties with feeding, partly psychologic, persisted. At 4½ years the girl weighed only 980 Gm. more than she had weighed twenty-four months earlier and had grown only 8.5 cm. during the same period. The blood pressure was 90 mm. systolic and 60 mm. diastolic. The urine continued pathologic. The reaction was sometimes alkaline, sometimes acid. It contained no reducing substance. The specific gravity varied under test conditions between 1.001 and 1.028. The outer table of the skull manifested a peculiar worm-eaten sort of rarefaction. Although the child clamored frequently for liquids, the intake of fluid was measured to be only 200 to 300 cc. daily. The volume of urine approximated 1,000 cc. per twenty-four hours. Cystine was demonstrated several times by qualitative tests. A single estimate gave a concentration of 1.5 mg. per hundred cubic centimeters and a total twenty-four hour excretion value of 9 mg. The calcium content of the serum varied between 9.4 and 11.8 mg. per hundred cubic centimeters and the inorganic phosphorus content between 2.8 and 4.1 mg. Recrudescence of rickets was effectively controlled by the use of irradiated ergosterol daily for three and a half months.

The administration of yeast appeared to exert temporary benefit on appetite and weight.

The brother weighed 3.2 Kg. at birth. There were no nutritional difficulties. Rickets became apparent at 8 months. At 16 months skeletal deformity was severe. Vigorous treatment with vitamin D and sunlight yielded no evident benefit. At 18 months the roentgenogram showed florid rickets. The urine contained albumin, leukocytes and granular casts. At 28 months the boy was 81 cm. in height and weighed 10.6 Kg. Vitamin D *Stosstherapie* (treatment in intermittent courses) had been practiced just before he was submitted to detailed examination. This was thought to account for the facts that the calcium content of the serum was 10.8 mg. and the inorganic phosphorus content 4.8 mg. per hundred cubic centimeters. Increased maturity of carpal ossification was also evident. After two months the phosphorus level declined to 3.9 mg.; the calcium content remained normal.

There was considerable hypertension, the systolic blood pressure being 120 and the diastolic 90 mm. of mercury. The heart was not enlarged. The blood nonprotein nitrogen was 23.1 mg. per hundred cubic centimeters. The urine was usually acid, rarely neutral. The specific gravity varied between 1.001 and 1.030. There was no sugar. Intravenous urography revealed that the pelvis of the right kidney was of normal outline; that of the left kidney was not well visualized.

Qualitative tests of the urine failed to reveal the presence of cystine. The quantitative procedure of Fujita and Numata [54] disclosed a concentration of 9.75 mg. per hundred cubic centimeters, equivalent to a daily excretion of 29.3 mg. The oral ingestion of 0.5 Gm. of cysteine caused the excretion of 0.051 Gm. of cystine during the first twenty-four hours thereafter and of 0.042 Gm. during the second and 0.038 Gm. during the third twenty-four hour period.

DANIS AND ROSSEN, 1941.[42]—*Case 1.*—The first patient, the brother of the second, was born at term, weighing 3.7 Kg. The father and mother were apparently healthy. The diet during infancy was of average composition, but the child received virtually no cod liver oil. At 7 months the first tooth appeared and the infant commenced to sit up. At 1 year he weighed 9.1 Kg. and appeared well. After an attack of chickenpox at 17 months he ceased to grow, exhibited abnormal thirst and poor appetite and lost much weight.

At 22 months his height was 70 cm. and his weight 7.1 Kg. Malnutrition and rickets were apparent. The skin was pale and yellowish and the muscles atrophic. The systolic blood pressure was 80 mm. and the diastolic 60 mm.

The urine contained sugar (2 plus), acetone (2 plus), a trace of albumin, granular and hyaline casts, and 6 to 10 white blood cells and 2 to 3 erythrocytes per high power field. The specific gravity varied between 1.002 and 1.006 throughout day and night.

The concentration of nonprotein nitrogen in the blood was 32 mg., of calcium 8.1 mg., of phosphorus 6.1 mg., of chloride 460 mg. and of protein (serum) 9.6 Gm. per hundred cubic centimeters. On three occasions intravenous injection of skiodan failed to visualize the kidneys. Excretion of phenolsulfonphthalein was reduced to 14 per cent of normal.

The fasting blood sugar was determined three times during a period of two years; the values were 143, 100 and 96 mg. per hundred cubic centimeters. The duration of the fast which preceded the determinations was not specified. Tests

54. Fujita, A., and Numata, I.: Ueber die kolorimetrische Bestimmung von Cystein und Cystin, Biochem. Ztschr. **300**:264, 1939.

of the dextrose tolerance, carried out by a technic which was not described, showed a rise of blood sugar to approximately 200 mg. at the end of the first hour, with a decline to about 160 mg. at the end of the second hour and final values in the neighborhood of 100 mg., at the end of the fourth hour.

Two months after the original investigation tetany developed; the "blood" calcium was 8.6 mg. and the "blood" phosphorus 6.6 mg. Although the excretion of phenolsulfonphthalein was again found to be much reduced, the nonprotein nitrogen remained normal. Several months later the child contracted pertussis. During the illness there was an episode of coma. At that time the nonprotein nitrogen rose to 65 mg. per hundred cubic centimeters.

Approximately two years after the initial investigation the clearance of phenolsulfonphthalein remained reduced. The fasting blood sugar was 80 mg. per hundred cubic centimeters, and the results of a test of the dextrose tolerance were more nearly normal. Death occurred shortly thereafter, when the child was about 4 years of age. At that time the nonprotein nitrogen was 60 mg., the calcium 8.1 mg. and the phosphorus 4.9 mg. per hundred cubic centimeters of blood.

Autopsy revealed irregularities of the zone of preparatory calcification together with some fibrosis of the marrow cavity. The authors did not interpret these observations in detail but conveyed the implication that they were confirmatory of the clinical diagnosis of rickets. The liver was apparently normal. There was slight fibrosis of the pancreas and slight thickening of the medium-sized arterioles; the parenchymatous cells appeared normal. The kidneys were considerably reduced in size, and the capsule could be stripped only with difficulty, revealing finely granular, pale surfaces. No cysts were present. The cortex was greatly reduced and the medullary zone moderately diminished in thickness. Microscopic examination revealed hyalinization of about 8 per cent of the glomeruli. In many places the glomerular capsule was thickened and the capillary tufts adherent. The medium-sized arterioles showed moderate medial fibrosis. There was considerable variation in the size of the convoluted tubules. Many hyaline casts were seen. The tubular epithelium was swollen, pale and vacuolated. Finally, there was much fibrosis of the supporting structures.

Case 2.—The second patient, an elder sister of the first child, was found to be suffering from a similar malady but to a less severe degree. She had been healthy during the first year of life and developed normally. During the second summer she had an attack of diarrhea and contracted chickenpox.

At the age of 3 years she was 74 cm. in length and weighed 8.6 Kg. There were slight beading of the ribs, marked genu valgum, increased prominence of the forehead, muscular weakness and moderate anemia. The systolic blood pressure was 90 mm. and the diastolic 70 mm.

Roentgen examination revealed slight haziness of the diaphysis and retarded ossification of the carpal centers.

The urine contained sugar (1 plus), a trace of albumin and granular casts. The specific gravity was restricted to a range between 1.001 and 1.006. Cystoscopic examination demonstrated moderate dilatation of the ureter and of the pelvis of each kidney.

The nonprotein nitrogen content of the blood was 31 mg. per hundred cubic centimeters, the calcium content 8.9 mg., the phosphorus content 4.5 mg., and the protein content of the serum 6.7 Gm. During the next few months a slight increase of urinary volume, which had been present before, developed into definite polyuria with corresponding intensification of thirst. Growth continued at a slow rate. The child survived an attack of tetany, which was accompanied by

a "blood" calcium level of 6.9 mg. per hundred cubic centimeters and a "blood" phosphorus level of 5.2 mg. During the ensuing six years the excretion of phenolsulfonphthalein decreased from an initial value of 30 per cent of normal to 5 per cent, while the nonprotein nitrogen content of the blood rose as high as 85 mg. per hundred cubic centimeters. The blood calcium remained at approximately 9 mg. and the phosphorus in the neighborhood of 4 to 5 mg. per hundred cubic centimeters.

On three occasions within a period of five years the fasting blood sugar was found to be 95, 87 and 82 mg., respectively. Tests of the dextrose tolerance—in this case, too, an unspecified amount of test material being employed—revealed a hyperglycemic response with prolongation of the time required for the blood sugar to return to normal. The results of the later tests were less abnormal than that of the test performed at the time of the initial investigation.

Following the suggestion of Goldmann and Ekstein, trial was made of a diet purporting to have a content of potassium high in relation to that of sodium. The diet was described as consisting principally of bananas and potatoes, with little meat permitted. While the consequences were reported as gratifying, it was admitted that the nonrecurrence of subsequent attacks of tetany—apparently the most conspicuous benefit—might have been due to the natural variability of the disease.

Danis and Rossen interpreted the glycosuria exhibited by their patients as an expression of mild diabetes. This opinion appears to have been based on the fact that hyperglycemia and prolongation of the rise of blood sugar were encountered in tests of the dextrose tolerance. Although a fasting blood sugar content of 143 mg. was encountered in the first test of the boy, other values for both patients were in the neighborhood of 100 mg. The amount of dextrose employed in the tests was not stated. Furthermore, a diabetic type of dextrose tolerance curve is not uncommon in states of malnutrition. It is unfortunate for the critical appraisal of the cases that there is no record of the level of blood sugar at which glycosuria appeared or disappeared.

HOTTINGER, 1941.[43a]—*Case 1.*—The patient was born of healthy nonconsanguineous parents. He had 2 healthy brothers. From the end of the first year of life onward physical and functional development slowed appreciably and the boy showed excessive thirst, combined with frequent vomiting of solid food. The detection of a reductant in the urine led to a diagnosis of diabetes mellitus.

At 20 months he weighed 7.5 Kg. and was pale, sick, undernourished and dry looking. Physical and roentgen evidence of severe rickets was present. The volume of the urine was 600 cc. in twenty-four hours; it contained a trace of albumin. A substance was present which gave 2 plus reduction of Trommer's, 1 plus reduction of Fehling's and questionable reduction of Nylander's reagent; a quantitative test revealed a concentration of 0.5 per cent, expressed as sugar. There was a trace of acetone but no acetoacetic acid. The sediment was normal. The calcium content of the serum was 11.5 mg. and the sugar content of the whole blood 73 mg. per hundred cubic centimeters. A short time later the boy weighed 7.8 Kg. and was 75 cm. in length. Physical features of rickets gradually became less conspicuous, but pallor and abdominal distention persisted. During the next two years the following observations were made: The systolic pressure was 150 mm. of mercury and the diastolic 90. The blood sugar was 64 mg., the nonprotein nitrogen 29.3 and the urea nitrogen 15 mg. per hundred cubic centimeters. Creatinine was increased, and chloride was normal in amount.

The serum calcium was 9.2 mg. and the serum inorganic phosphorus 7.2 mg. per hundred cubic centimeters. The boy drank up to 2 or 3 liters of liquid daily; the specific gravity of the urine did not rise above 1.008. A trace of albumin persisted; bacteria, erythrocytes, leukocytes and a few granular and hyaline casts made their appearance. Under the influence of *Stosstherapie* with vitamin D the rickets healed temporarily.

At 6 years the weight was 11.6 Kg. and the height 90 cm. The blood pressure was moderately but variably elevated; the urine contained albumin, a few red cells and casts but no reductant or ketones. The maximum specific gravity was 1.010. The serum calcium varied in the neighborhood of 9 mg. per hundred cubic centimeters, the inorganic phosphorus between 7 and 8 mg. and the nonprotein nitrogen between 84 and 127 mg. Chlorides were reduced. The phosphatase activity was found to be 7.4 Bodansky units. The urine was tested for cystine with negative results.

At 7 years diffuse clouding of the cornea was noticed by the parents (See Bürki [43c]). Roentgen examination revealed recrudescent rickets combined with osteoporosis and osteosclerosis. Six months later epistaxis was followed by anuria, edema and convulsions. The liver and spleen were much enlarged and hard. The systolic blood pressure was elevated to 170 and the diastolic to 140 mm. The urine contained much albumin, many erythrocytes, some acetone, a few casts and a reducing substance, which, expressed as sugar, amounted to 0.2 per cent. The sugar content of the blood was 96 mg. per hundred cubic centimeters, the nonprotein nitrogen content 129 mg., the calcium content (serum) 5.12 mg., the inorganic phosphorus content 9.45 mg. and the total protein content 5.91 Gm. The phosphatase activity was again low, 4.51 Bodansky units. The terminal episode, which was ushered in by anuria and tetany, lasted only four days. Observations on the anion-cation balance of the blood and the urine were carried out. The results are not quoted here for the reason that they describe an agonal state and do not represent the biochemical features of the disease in any interpretable way. The only observation which appears relevant is that the ammonia-producing capacity of the kidneys was surprisingly unimpaired.

Autopsy disclosed diffused cystinosis. (The abstract of the anatomic examination was cited by Roulet [43b]).

From the enlarged liver Edelbacher isolated a considerable amount of cystine and showed by qualitative tests that cysteine was also present. This could not be crystallized.

Case 2.—Shortly after the death of the patient described in the foregoing report, the mother bore a girl, who appeared to be healthy in all respects. On the eighth day of life, while the infant was being fed exclusively at breast, the urine was examined, with results which were claimed to demonstrate the presence of cysteine. Inasmuch as the specimens were submitted to some deproteinizing procedure before being tested, the existence of preformed cysteine cannot be accepted as proved. Following oxidation, the specimens yielded cystine. Additional information concerning this patient is not available.

Roulet, 1941.[43b]—Autopsy of Hottinger's patient revealed dwarfism, undernutrition, enlargement of the liver and spleen, reduction of the size of both kidneys and in the skeleton evidence of both rickets and osteosclerosis. In addition, the cut surface of both the spleen and the liver showed yellow-white pleomorphic markings, more conspicuous in the former site than in the latter. Scrapings from the surfaces of both organs contained doubly refractile hexagonal

and rod-shaped crystals. The exterior of the kidneys presented a granular appearance due to the presence of many minute cysts. No concretions were encountered in the urinary tract. The parathyroid glands were not enlarged.

The histologic features were as follows: In the kidneys there was atrophy of both cortex and medulla. In the superficial layers the loss of interstitial tissue led to concentration of the glomeruli. The glomerular capsule and the capillary knots showed necrosis, fibrinous adhesions, hyaline sclerosis and epithelial proliferation. Whereas in some foci the changes were of moderate degree, they were mostly severe. The finer vessels were thickened. In the deeper portions of the cortex the interstitial tissues showed extensive fibrous hyperplasia. In this region the tubules were atrophic, showing in some places narrowing of the lumen with enlargement of the epithelium and in others a widened lumen with flattened epithelium; here and there casts were present. The tortuosity of the convoluted tubules was exaggerated. The features distinctive of the epithelium of various parts of the nephron were obliterated. Crystals were encountered in all zones of the kidneys. Their form was either hexagonal or that of an elongated prism; they were strongly doubly refractile. Most commonly they were included within large mononuclear cells, but occasionally they lay free within the interstitial tissues. Their number was greatest at the corticomedullary junction and near the hilus. In the cortex, where they were less numerous, they were frequently deposited in the region of a glomerulus or within the capsular endothelium.

The spleen contained crystals in greatest abundance; although most of them were included within macrophages, some lay free in the tissues. The size and appearance of the phagocytes and their content justified the designation "pseudo-foam cells"; the lymph nodes presented similar features.

The Kupffer cells of the liver and the tissues of Glisson's capsule contained numerous crystals. The normal architecture of the hepatic cells was preserved; they contained no crystals. Crystals were also found in the supporting tissues of the lungs, gastrointestinal tract, thymus and testes and within the bone marrow. They were absent from the thyroid, hypophysis and epiphysis cerebri, brain and spinal cord; a few were noted in the pia mater.

The results of examination of the skeleton can be summarized as follows: 1. Evidence of rickets, viz., irregular widening of the zone of proliferating cartilage with defect or complete absence of preparatory calcification and invasion of the cartilage by vessels entering from the marrow. The primary trabeculae were frequently absent; when present they were surrounded by a broad band of osteoid tissue. Islands of poorly calcified cartilage persisted within the metaphysis at some distance from the epiphysis. 2. Extensive resorption of the previously calcified trabeculae of the spongiosa. In some places osteoblasts were numerous. In others the trabeculae appeared to be penetrated and dissected by fibrous tissue, with loss of mineral and collapse of trabeculae to the point of composing a picture reminiscent of the mosaic structure peculiar to Paget's disease. 3. Osteosclerosis. In the proximal portions of the femur and humerus many of the trabeculae were large and coarse. This was interpreted to be due to the mineralization of the large fingers of cartilage which had failed to undergo remodeling into the conformation of normal trabeculae.

BÜRKI, 1941.[43c]—The clinical and pathologic observations relating to the eyes of Hottinger's patient are of particular interest. The corneas appeared steamy. The slit lamp revealed glittering points of light uniformly distributed throughout the anterior zone of the cornea between Bowman's and Descemet's membranes.

Fortyfold magnification resolved the scintillas into minute angular or needle-like structures. Vision was reduced in both eyes and conjunctival sensation somewhat impaired. Maceration of a bit of corneal tissue removed at biopsy disclosed crystals which were morphologically suggestive of uric acid or urates. Microchemical tests suggested, by exclusion, the possibility of cystine, but the quantity of material was too small to permit qualitative identification of sulfur. Postmortem examination of the entire eye revealed the presence of crystals in the cornea, conjunctiva, uveal tract and episclera and in lesser amount within the sclera. The lens, vitreous and retina were free. Chemical examination showed the crystals to be composed of cystine.

Special Reports

Reports of Subcommittees of British Paediatric Association

BREAST FEEDING IN RELATION TO FEMALE LABOR AS IT AFFECTS BIRMINGHAM

After a request from the executive committee of the British Pediatric Association in July 1942, a committee was formed to investigate breast feeding in the city of Birmingham, with special reference to its relation to female labor. We of the committee are greatly indebted to the health visitors (100) working in the department of maternity and child welfare. These visitors were asked to report on the babies born during the first quarter of 1941 and the first quarter of 1942.

Each health visitor was given a form setting out the information required, as detailed in the questionnaire, as follows:

Questionnaire Form to Cover Return

First or later child?
Period of breast feeding?
Mother working or not during pregnancy?
If so, how long?
Mother working after confinement?
If so, how soon?
If not, is she anxious to commence or does she wish to postpone her return until the normal breast feeding period is over?

Each visitor also received a personal explanation from the superintendent of health visitors in regard to the exact requirements, special emphasis being given to the reasons why the information was wanted, in order to obtain enthusiastic cooperation. The schedules were to be returned within six weeks. At the end of the period, schedules which had not been sent in were looked up, and a certain number had to be returned for further information. The superintendent of the health visitors incorporated the schedules to obtain the figures utilized in this report. We emphasize that this required considerable extra efforts in the health visitor's work. Records of 4,635 babies were obtained.

In addition to the statistics some comments are included, which were obtained in a personal discussion by Dr. Cassie at a general meeting of health visitors; the observations set out were unanimous.

NOTES ON DISCUSSION WITH SUPERINTENDENT OF HEALTH VISITORS, FEB. 19, 1942

1. The incidence of breast feeding is not materially affected by the present situation.

In the areas where married women were not accustomed to working in the factories they are not going into the factories while they have a baby under 1 year.

In the areas where they were accustomed to working before the war, the women go out as before, but usually at no earlier date; i. e. they wait until the baby is 2 months old at least.

This is borne out by the admissions to wartime nurseries. Young babies are coming in very small numbers. It is only in poor districts that the number of babies is more than one fifth of the total. Even there, it is rare to have an infant under 3 months.

2. Present influences which are adverse to breast feeding are:

(*a*) Waiting in line to shop.

(*b*) Emotional disturbances, particularly anxiety as to husbands.

(*c*) Part time work; liability to supplementary feeding.

(*d*) Physicians' advice. This, more than any other single factor, is still responsible for weaning babies. Physicians still take babies off the breast whenever there is any difficulty, rather than take the trouble to go into the whole difficult question of successful breast feeding. Physicians were named who make a practice of this.

Babies are doing well, better than before the war, and the general feeling is that the use of breast feeding has not declined.

Where the men are at home and engaged in munitions work, as they are in large districts of the city of Birmingham, there is more money going into the homes than usual; the women in such circumstances are disinclined to go out to work, and the infants are on the whole better cared for than in the past.

A further inquiry was made by Dr. Pierce in the outpatient department of the Birmingham Children's Hospital, and her findings are included in the report.

It should be stated that a prior inquiry was made in 1938 in reference to babies born from January to June 1937. A copy of these statistics are included in this report (table 1).

It is interesting to note that the incidence of breast feeding (wholly or partly) for three to six months was 51 per cent, whereas in the 1941 and 1942 inquiry it was practically the same, 53 per cent. This indicates that in the prewar periods there appears no obvious factor altering the incidence of breast feeding to any appreciable degree. Some observations were made in 1938 in regard to the reason for the limited incidence of breast feeding or for its abandonment. Table 2 indicates the details.

It will be noted that in the 1939 series 15 per cent of the mothers gave up breast feeding because of going to work. In the present series only 11 per cent reported a similar reason. This would seem to be a reflection of the diminished financial embarrassments in the families of munitions workers.

TABLE 1.—*Breast Feeding Record of Children Born January to June 1937 (Children Living January 1938)*

		Inner Circle of City (12-Centers)	Outer Circle of City (21 Centers)	Totals	Percentage of All Babies of Corresponding Age
Total number reported by health visitors...		2,023	2,355	4,378	
Breast fed					
1 month or less	Wholly.....	1,543	1,855	3,398	
	Partly.....	206	225	431	
				3,829	87
1 to 2 months	Wholly.....	1,162	1,355	2,517	
	Partly.....	262	372	634	
				3,151	72
2 to 3 months	Wholly.....	914	1,094	2,008	
	Partly.....	295	304	599	
				2,607	60
3 to 6 months	Wholly.....	751	881	1,632	
	Partly.....	283	336	619	
				2,251	51
Children not breast fed at first visit, 549, or 13% of total					

TABLE 2.—*Breast Feeding Record of Children Born January to June 1937*

Cause of Abandoning Breast Feeding	Inner Circle of City (12 Centers)		Outer Circle of City (21 Centers)		Totals	
	No.	%	No.	%	No.	%
1. Illness of mother.....	263	24	264	23	526	23
2. Anxiety of mother concerning progress of child.....	303	28	430	37	733	33
3. Mother going to work.....	224	21	113	10	337	15
4. Other causes.....	299	27	348	30	647	29
Totals.....	1,088		1,155		2,243	

Comparison shows that in the earlier weeks the first baby is at a disadvantage as compared with the second or later baby but after two months this difference disappears. This may bear some relation to a lesser degree of maternal anxiety in the second or later pregnancy.

Working in pregnancy appears to have little influence in regard to subsequent breast feeding. It is interesting to note that only a small proportion of mothers are anxious to return to work, and these are mainly unmarried mothers or women in key positions. The actual members returning to work are small and amount to only approximately 12 per cent.

Since only 12 per cent are working after confinement, it appears that women as a whole prefer to stay at home with their infants when economic circumstances are favorable. There is corroborative evidence of this in Dr. Pierce's observations. The same point is revealed in the small number of young infants admitted to day nurseries, although they are accepted from the age of 1 month. It has been noted that the only nurseries to which the larger number of infants are admitted are situated in the districts where the women were accustomed to go out to work before the war and, incidentally, where the infant mortality rates were high.

SPECIAL COMMENTS ON TABLE 2

The table as set out shows the following points of interest:

1. *The Percentage of Infants Either not Breast Fed or Breast Fed for Less Than One Month.*—The weaning of these infants took place before the health visitor was able to exert any influence on the result and therefore occurred under the influence of the physician or midwife. In 1941 the percentage was 7.9 per cent, and in 1942 it was 7.2 per cent. It is believed that a high percentage of the mothers were unmarried. There is a comparable figure available for Birmingham. It was found that in 1938 13 per cent of the infants were not breast fed at the age of 1 month; hence the present result is actually much better than in the past.

The improvement among the group of married mothers is greater still, since there has been a definite increase in illegitimate births.

Illegitimate Births in Birmingham, First Quarter

Year	No.
1938	180
1939	178
1940	176
1941	169
1942	239

2. *The Total Number of Babies Fed Up to and Over Three Months.*—In 1941 53 per cent of the infants were fed for at least three months, and in 1942, 52 per cent. This figure shows no material difference from the results obtained in the 1938 inquiry, when it was found that 51 per cent of the children were still on the breast from three to six months.

These figures suggest that more breast feeding is being carried out at the present time than before the war. This may be associated with better economic conditions in many homes.

The difference between the first and later infants is not material. Only 15 cases were definitely cited in which a mother who had not fed her first infant at breast was successful with a later child. One would,

TABLE 3.—*Investigation of Breast Feeding, 1942*

		Percentage of Children	Number of Children	Mother Working in Pregnancy: Up to 24 Weeks	Up to 28 Weeks	Up to 32 Weeks	Over 32 Weeks	Total	Anxious to Return to Work	Mother Working After Confinement: First month	Second Month	Third Month	Later	Total
First Quarter of 1941 (Total Number Investigated, 1,937)														
Not breast fed or for less than 1 month	First baby	10	100	10	1	..	1	12	8	1	1	3	7	12
	Second or later children	5.4	51	5	..	..	..	5	5	..	4	..	2	6
Breast fed up to 1 mo.	First baby	27	274	28	13	7	5	53	22	6	3	9	23	41
	Second or later children	22	207	14	7	2	1	24	19	2	1	3	12	18
Breast fed up to 2 mo.	First baby	13	129	21	8	4	6	39	13	..	1	6	8	15
	Second or later children	15	141	9	9	1	1	20	9	..	5	1	10	16
Breast fed up to 3 mo.	First baby	11	114	23	9	1	..	33	10	..	..	4	10	14
	Second or later children	11.5	108	11	1	1	..	13	5	..	1	..	9	10
Breast fed over 3 mo.	First baby	38	384	46	23	11	2	82	18	1	4	4	47	56
	Second or later children	45	429	18	11	2	4	35	24	..	2	13	45	60
Total investigated	First babies (1,001) Later babies (936)	..	1,937	185	82	29	20	316	133	10	22	43	173	248 (12%)
First Quarter of 1942 (Total Number Investigated, 2,698)														
Not breast fed or for less than 1 month	First baby	8	111	9	8	..	..	17	9	1	7	2	3	13
	Second or later children	6.4	85	2	2	2	2	8	6	1	7	2	2	12
Breast fed up to 1 mo.	First baby	29	390	52	24	10	9	95	31	5	16	12	20	53
	Second or later children	24.6	324	17	7	12	7	43	17	5	12	3	24	44
Breast fed up to 2 mo.	First baby	14.2	196	52	23	4	1	80	22	2	5	6	17	30
	Second or later children	14.3	189	20	10	3	5	38	18	1	10	3	8	22
Breast fed up to 3 mo.	First baby	10.3	142	24	13	5	1	43	24	..	2	5	8	15
	Second or later children	11.7	155	11	7	2	..	20	12	..	..	2	13	15
Breast fed over 3 mo.	First baby	39	543	83	35	13	4	135	34	1	2	7	46	56
	Second or later children	42.7	563	39	23	8	8	78	39	3	1	10	42	56
Total investigated	First babies (1,382) Later babies (1,316)	..	2,698	309	152	59	37	557	212	19	62	52	183	316 (11%)

SUMMARY OF TABLE 3

Total number of cases investigated first quarter of 1941	1,937
Total number of cases investigated first quarter of 1942	2,698
Grand total investigated	4,635
Previous child not breast fed, but successful with later child	15
1941 Total not breast fed or breast fed for less than 1 month	7.9%
1942 Total not breast fed or breast fed for less than 1 month	7.2%

	1941 No.	1941 %	1942 No.	1942 %
First babies fed up to and over 3 months	498	49.7	685	49.5
Second babies fed up to and over 3 months	537	57.3	718	54.5
Total	1,035	53.4	1,403	52.0

Mothers working	1941	1942
Before confinement	16.3%	20.6%
After confinement	12.8%	11.7%
Anxious to work	6.8%	7.8%

Day nurseries (babies under 6 months in attendance in second quarter of 1942)*

Under 2 months of age	18
Between 2 and 3 months	29
Between 3 and 4 months	33
Between 4 and 5 months	98
Total	178

* Only two mothers out of this number have attended the nursery to breast feed their baby.

of course, expect some improvement with the second and subsequent children.

3. *Work in Relation to Breast Feeding.*—It is surprising to find the small percentage (16 per cent) of women actually working during pregnancy. This percentage is further decreased when the figures for the earlier weeks are omitted. Only 2 per cent were working after twenty-eight weeks of pregnancy. The influence of the work during pregnancy can be considered to have little effect on the final totals.

4. *Weaning Due to Anxiety to Return to Work.*—It was repeatedly emphasized that this was mainly among the unmarried mothers.

5. *Weaning the Child in Order to Return to Work.*—Only a comparatively low percentage of mothers return to work after confinement until the child is over the age of 6 months; it is rather when the child is weaned that the mother thinks of working. As long as the child is thriving on the breast, she does not consider the question seriously.

REPORT OF DR. MILA PIERCE

The report of Dr. Pierce is concerned with 164 babies brought to the casualty and outpatient department of the Children's Hospital. The contrast between the details of her report and those of the welfare department emphasizes the fact that these figures are taken from a specially selected group of the baby population. In view of this, independent comment is made regarding Dr. Pierce's observations.

Following is an analysis of an inquiry regarding the duration of breast feeding of babies brought to the outpatient department of the Birmingham Children's Hospital during September 1942. It is submitted in spite of the small number of cases, since it represents a different cross section of the baby population of the city than that of the welfare group.

1. *Number of Babies Included in the Survey.*—The infants were distributed as follows:

	No.
First born	80
Second born	39
Third born or later siblings	45
Total	164

2. *Selection of Subjects.*—Consecutive babies under 1 year of age seen in the casualty office and in the surgical clinic were included in the survey. They fall into two groups, the "sick" and the "well," and the findings are analyzed with this in mind.

The "sick" babies are those whose presenting complaint was such that it affected the general health and nutrition. The "well' group are those whose complaint did not affect their general well-being.

A. Diagnosis

Sick Babies	No.	Well Babies	No.
Gastroenteritis	39	Cutaneous, naevus	49
Infections of upper respiratory tract and otitis	21	Phimosis	26
Cutaneous infections	10	Clubfoot	9
Whooping cough	2	Hernia	4
Abscesses	2	Total	88
Nephritis	1		
Anemia	1		
Total	76		

B. Age at Date of Interview

(1) Actual average age

88 well babies	4 months 27 days
76 sick babies	4 months 4 days
164 total group	4 months 15.5 days

(2) Range (in months)

Age At Date of Interview for Well and for Sick Babies

Age	Well Babies		Sick Babies	
	Number	Percentage	Number	Percentage
Birth to 2 weeks	..	.....	..	.....
2 to 4 weeks	2	2.27	3	3.94
1 to 2 months	6	2.81	17	22.36
2 to 3 months	15	17.04	11	14.47
Total number and percentage under 3 months	23	26.12	31	40.77
3 to 4 months	11	12.50	8	10.50
4 to 5 months	17	19.31	7	9.21
5 to 6 months	8	9.09	7	9.21
Total number and percentage under 6 months	59	67.02	53	69.71
6 to 9 months	18	20.45	11	14.47
Total number and percentage under 9 months	77	87.47	64	74.18
9 to 12 months	11	12.50	12	15.79
Total number and percentage under 1 year	88	99.97	76	99.97

Of the sick infants, 40 per cent were under 3 months of age and 69.71 per cent under 6 months; the number over 6 months was small, equaling 30 per cent of the whole. As compared with well babies, the proportion is similar over 6 months, but of babies under 3 months, there is a marked preponderance of sick babies; this is equalized in a 3 to 6 month group.

3. *Duration of Breast Feeding.*

Time at Which Baby was Weaned from Breast

Weaned at Age	Well Babies		Sick Babies	
	Number	Percentage	Number	Percentage
Never put to breast	11	12.50	8	16.52
2 weeks or earlier	5	5.68	7	9.21
		18.18		19.73
2 to 4 weeks	..	15.90	22	28.94
		34.08		48.67
1 to 2 months	17	19.23	18	23.68
2 to 3 months	11	12.5	6	7.89
Percentage weaned by end of 3 months	..	65.81	..	80.24
3 to 4 months	10	11.36	3	3.94
4 to 5 months	8	9.09	4	5.26
5 to 6 months	3	3.40	4	5.26
Percentage weaned by end of 6 months	..	89.86	..	94.68
6 to 9 months	3	3.40	2	2.63
Percentage weaned by end of 9 months	..	93.26	..	97.31
9 to 12 months	6	6.81	2	2.63
Percentage weaned by end of 1 year	88	99.86	76	99.94

It will be seen that an equal proportion of sick and of well babies were weaned in the first fortnight. In the next fortnight the sick babies led by 14 per cent. This continued until the end of the third month. The proportion thereafter was equalized.

4. *Comparison of Duration of Breast Feeding in Groups of Babies with Gastroenteritis and in Sick Babies with Other Conditions.*

Total number of babies with gastroenteritis	39
Total number of sick babies with other conditions	37
Total number of sick babies	164
Actual average age of babies with gastroenteritis	1 month 3 days
Actual average age of other sick babies	1 month 21 days

Age at Date of Interview for Babies with Gastroenteritis and for Other Sick Babies

Age at Date of Interview	Babies with Gastroenteritis		Other Sick Babies	
	Number	Percentage	Number	Percentage
0 to 2 weeks	0	.....	0	.....
2 to 4 weeks	0	.....	3	8.10
Percentage under 1 month	..	.....	..	8.10
1 to 2 months	10	25.64	7	18.91
2 to 3 months	10	25.64	1	2.70
Percentage under 3 months	..	51.28	..	29.71
3 to 4 months	2	5.12	6	16.21
4 to 5 months	4	10.25	3	8.10
5 to 6 months	3	7.68	4	10.81
Percentage under 6 months	..	74.33	..	64.83
6 to 9 months	4	10.25	7	18.91
Percentage under 9 months	..	84.58	..	83.74
9 to 12 months	6	15.39	6	16.21
	39	99.97	27	99.95

The higher proportion of young infants suffering from gastroenteritis as against other conditions is evident. This preponderance is lost after the sixth month.

Duration of Breast Feeding (76 Sick Children)

Weaned at Age	Babies with Gastroenteritis		Other Sick Babies	
	Number	Percentage	Number	Percentage
0 to 2 weeks	8	20.51	7	18.91
2 to 4 weeks	13	33.34	9	24.32
Percentage weaned by end of first month	..	53.85	..	43.23
1 to 2 months	10	25.64	8	21.62
2 to 3 months	4	10.25	2	5.40
Percentage weaned by end of third month	..	89.74	..	70.25
3 to 4 months	..	.....	3	8.10
4 to 5 months	1	2.56	3	8.10
5 to 6 months	1	2.56	3	8.10
Percentage weaned by end of sixth month	..	94.86	..	94.55
6 to 9 months	2	5.12	..	.....
Percentage weaned by end of ninth month	..	99.98		
9 to 12 months	..	.....	2	5.40
	39	99.98	37	99.95

This table shows that gastroenteritis develops in a higher proportion (20 per cent) of babies weaned early. This preponderance disappears after the sixth month, when the incidence in the two groups is approximately equal.

Employment During Pregnancy

	No.	%
Total number of mothers, 164		
Number employed up to 24th week of pregnancy	12	7.4
Number employed up to 28th week of pregnancy	6	3.6
Number employed up to 32d week of pregnancy and later	11	6.7
Total number employed after six months of pregnancy	29	17.0

Employment During First Six Months after Birth of Child

	No.
Mothers returning to work before child was 2 weeks	1
Mothers returning to work before child was 1 month	0
Mothers returning to work before child was 2 months	1
Mothers returning to work before child was 3 months	2
Mothers returning to work before child was 4 months	1
Mothers returning to work before child was 5 months	3
Mothers returning to work before child was 6 months	2
Total returning to work before child was 6 months of age	10 (6.07%)

COMMENT ON DR. PIERCE'S REPORT

1. The duration of breast feeding in this group is considerably shorter than in the welfare group. In this group, 34.19 per cent of the well babies and 19.76 per cent of the sick babies were breast fed after the third month, as compared with 49.5 per cent in the welfare group.

2. It is significant that babies in the sick group were weaned earlier than those in the well group; 48 per cent were weaned by the end of the first month and 80 per cent by the end of the third month, as contrasted with the well group, in which 34 per cent were weaned by the end of the first month and 45 per cent by the end of the third month. After the sixth month there is no striking difference in the period of weaning of the two groups.

3. The group of "sick babies" is younger than the group of "well babies," but there is no evidence that the onset of symptoms of the current illness played a role in the period of weaning.

4. The babies with gastroenteritis were weaned somewhat earlier than either the "well babies" or the babies ill with other complaints; 53 per cent were weaned by the end of the third month, as compared with 43 per cent of other sick babies weaned at the same period.

5. The percentage of mothers employed during pregnancy was similar to the figure for the welfare group, i. e. 17 per cent in the former as compared with 16.3 per cent in the latter.

6. The number of mothers employed during the early months after the baby's birth was lower (6 per cent as compared with 12.8 per cent).

CONCLUSIONS DRAWN FROM DR. PIERCE'S REPORT

1. Early weaning is related to the occurrence of gastroenteritis.

2. Early weaning is associated with early infections.

3. There is no suggestion from these figures for Birmingham that weaning is associated with the mother's employment.

4. The usual reason given for weaning is failure of milk.

5. The observer gained the impression that the large majority of mothers in both groups were in poor general health, exhibiting pallor, caries, poor skin tone, nervousness and conduct fatigue. The observer has had a wide experience with a similar group in Chicago and finds the lower standard of maternal general health striking but does not conclude that war causes are the chief factor.

WARTIME DAY NURSERIES

The following tabulation shows the observations obtained from 178 individual inquiries.

Babies weaned for the following reasons:

Day Nurseries (October 1942)	Total No.
Milk failed (59%)	85
To allow mother to work (22%)	33
Illness of mother	3
No reason given	7
Doctor's orders	6
Abscess of breast	6
Illness of baby	2
Unmarried mothers *	2
Total	144
No report	34
Grand Total	178

* Baby not usually in wartime nursery.

It will be noted that a high percentage of mothers stated that their "milk failed." This would seem to indicate difficulties in the breast feeding. Of babies weaned to allow the mother to work, the information must be taken in conjunction with the rising number of unmarried mothers. Although only 2 mothers are noted as unmarried, the fact that a child is illegitimate is not necessarily known at the nursery.

FINAL CONCLUSIONS

1. In the opinion of this subcommittee wartime conditions have not materially altered the incidence of breast feeding.

2. It is evident that few women are prepared to leave the home to go to work while the baby is under the age of 6 months.

3. The investigation emphasizes that only 50 per cent of women are prepared to continue breast feeding of the baby after three months.

Dr. Ethel Cassie (co-opted)

Dr. Frances Braid (co-opted)

Dr. Mila Pierce (from Chicago) (co-opted)

Dr. A. V. Neale.

October 1942.

DOSAGE OF VITAMIN D

1. OPINIONS ON VITAMIN D REQUIREMENTS OF INFANTS AND CHILDREN

(*a*) The minimum requirement for infants and children is not known.

(*b*) The Technical Commission on Nutrition of the League of Nations[1] (1938) placed the requirements of infants at 400 to 500 international units daily.

(*c*) The Committee on Food and Nutrition of the National Research Council of the United States of America and the Committee on Vitamins of the American Academy of Paediatrics (Dann & Davison,[2] 1942) put the requirements of children from birth up to 15 years of age at 400 to 800 international (U. S. P.) units daily.

(*d*) The figure in (*c*) has been endorsed by the National Nutrition Conference for Defense[3] (1941), summoned by President Roosevelt.

(*e*) Park and Eliot[4] (1942) consider that 800 to 1,000 international (U. S. P.) units daily covers any possible requirement of full term infants.

(*f*) At St. Bartholomew's Hospital, London, for the last ten years, it has been the practice to give daily doses of 600 international units as cod liver oil to infants prophylactically.

(*g*) Premature infants (i. e. infants whose birth weight is below 5½ pounds [2,500 Gm.]) vary more widely in their individual requirements than full term infants, but their need is uniformly higher. Their daily routine allowance should be twice that of full term infants and should be continued at this rate until their second birthday.

(*h*) The incidence of active rickets is as great under 6 months of age as over. In view of the more rapid growth in the earlier months of life, the prophylactic requirement of vitamin D is greater in these months.

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1. Report by the Technical Commission on Nutrition on the Work of Its Third Session, Bull. Health Organ., League of Nations **7**:460, 1938.

2. Dann, W. J., and Davison, W. C.: Nutritional Requirements of Children, Am. J. Dis. Child. **63**:366 (Feb.) 1942.

3. National Nutrition Conference, Pub. Health Rep. **56**:1233, 1941.

4. Eliot, M. M., and Park, E. A., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 1, chap. 36, p. 97.

(*i*) In summer in Great Britain, sunshine and skyshine can generally be relied on to protect full term infants from rickets, provided they are suitably exposed to these elements for at least four hours daily. This provision cannot, however, be expected to be uniformly available, especially under the difficult conditions of wartime. In winter, little vitamin D is rendered available by natural irradiation. This subcommittee therefore considers that seasonal variations in the allowance of vitamin D would be unwise.

(*j*) With regard to children beyond the age of infancy who are receiving a mixed diet the amount of vitamin D obtainable from their food is subject to such variation and in any case is so small that a deduction in the amount of vitamin D supplement is considered to be unjustified.

(*k*) With regard to infants, this report does not distinguish between those who are breast fed and those artificially reared, the subcommittee being of the opinion that a supplementary ration of vitamin D should be issued impartially to both groups of infants, irrespective of whether or not nursing mothers are to be allowed a vitamin D supplement.

2. THE PRESENT OFFICIAL DOSAGE OF "COD LIVER OIL COMPOUND"

The cod liver oil compound supplied by the government as a supplementary ration for children under 5 years of age contains "not less than 100 international units of vitamin D per gram." The maximum dosage for children under 6 months old is "half a teaspoonful daily," and for those over 6 months, "1 teaspoonful." On a generous interpretation, this provides 200 international units daily for infants under 6 months of age and 400 international units daily for older infants. It would be hard to find any authority with clinical experience to support so small a dose. Moreover, it will be noted that infants under 6 months are allowed a smaller dose than older babies, which does not accord with their actual needs.

3. RECOMMENDATIONS CONCERNING DOSAGE OF VITAMIN D

A daily allowance under the government scheme should be sufficient to protect practically all babies under the varying circumstances of their lives, without further addition of vitamin D obtained through private channels.

(*a*) *Full Term Infants and Chlidren up to 5 Years Old.*—Although a daily intake of 500 international units would probably protect the majority of full term infants and young children, a daily allowance of 700 international units would give a wider margin of safety. For simplicity in administration, a "vitaminized" oil should be so reenforced with irradiated ergosterol that 1 fluidrachm (3.7 cc.) contains the daily

allowance of 700 international units as well as the 3,500 international units of vitamin A now provided in each fluidrachm.

(*b*) *Premature Infants (Under 5½ Pounds at Birth) from Birth to 2 Years.*—The allowance should be double that in paragraph 3 (*a*), i. e. a daily allowance of 1,400 international units contained in 2 fluidrachms (7.4 cc.) of "vitaminized" oil.

(*c*) *School Children.*—Information regarding the vitamin D needs of school children is meager, although there is much to suggest that vitamin D deficiency is one factor in the causation of dental caries in school children. Taking also into consideration the small amount of fat, fish, eggs and meat fat that are available, it is recommended that a supplement of 3,500 international units of vitamin D per week be allowed for this group of children. Administratively, this supplement might be issued with school milk or through the medium of school dinners.

(*d*) *Pregnant and Nursing Women.*—It is recommended that a supplement of 700 international units of vitamin D daily be allowed to this group of the community. The provision of such a supplement should not do away with the supplement for breast-fed infants.

4. SUGGESTIONS CONCERNING ROUTINE ADMINISTRATION OF VITAMIN D

Printed directions for the mother should be issued with the ration of vitamin D. These should:

(*a*) Instruct her to start giving the oil gradually, beginning with a few drops daily when the infant is a month old and taking a fortnight to work up to the full dose of 1 teaspoonful (700 international units daily).

(*b*) Inform her that for an infant whose weight at birth is over 5½ pounds (2,500 Gm.) the supplement of vitamin D need not be given on summer days provided the infant is out of doors morning and afternoon.

(*c*) Warn her that an infant whose birth weight is below 5½ pounds is particularly susceptible to rickets; that the allowance of vitamin D supplement must therefore be doubled to 2 teaspoonfuls daily, and that this should be divided into four equal doses each day and begun gradually; that this supplement should be given throughout summer and winter, and that all premature babies should be under regular medical supervision.

For the information of physicians, the composition and vitamin content of "cod liver oil compound" should be given on the label and published in the medical press.

5 RECOMMENDATIONS TO THE EXECUTIVE COMMITTEE OF THE BRITISH PAEDIATRIC ASSOCIATION AS TO PROCEDURE THAT MIGHT BE ADOPTED WITH REGARD TO THIS REPORT

(*a*) Assuming that the executive committee accept this report, it should be forwarded to the Minister of Health, the Minister of Food and the Minister of Education with a request for their cooperation in putting the recommendations into practice.

(*b*) Either the whole report or an abstract of the recommendations should be published in the medical press, including the public health journals, and be sent to the nursing journals.

(*c*) Copies should be circulated to the members of the British Paediatric Association and to the members of the Society of Medical Officers of Health.

DR. WILFRED SHELDON, CHAIRMAN
DR. CHARLES HARRIS
PROF. NOAH MORRIS
DR. HELEN MACKAY (co-opted)

NEONATAL MORTALITY

1. We wish to make it clear at the outset that when we speak of neonatal mortality we have also in mind (*a*) the no less important, though less sharply defined, question of neonatal morbidity and (*b*) the loss of potential lives by stillbirth. In regard to neonatal morbidity, it should be stressed that though young infants possess a remarkable power of recovery from trauma and illness failure to make full recovery is especially regrettable in early life, when each child should be entitled to the prospect of a long term of good health.

2. It is common knowledge that the gratifying decline in the infant mortality rate which has taken place in most countries during the last fifty years or more has not been accompanied by a correspondingly satisfactory fall of the neonatal mortality rate. Yet some countries and areas (e. g. the Netherlands, Australasia and the large cities of the United States of America) have been more successful in this respect than others (e. g. Scotland, England and Wales), which shows that the problem is not insoluble.

3. In studying neonatal mortality, it is important to view the particular epoch in its relation both to preceding events and to subsequent life. Without entering into detail, it is apparent that adverse influences may operate: (*a*) hereditarily; (*b*) during embryonic life (e. g. congenital malformations); (*c*) during fetal life (e. g. syphilis); (*d*) by premature expulsion of the fetus in an immature state; (*e*) during birth (e. g. birth trauma or failure of the physiologic readjustments consequent on birth), and (*f*) after birth, during the neonatal period (e. g. infection, lack of adequate nursing skill and care, or mismanagement or failure of breast feeding).

4. Thus it is obvious that the problems of neonatal mortality concern not only pediatricians, but obstetricians, general practitioners, general physicians and public health workers, and there is a need for close cooperation in study and practice. But the onus of leadership of the team should be accepted by the pediatricians, who are more intimately concerned than any other group.

5. In this report observations shall be restricted to the chief causes of neonatal mortality, which are: (*a*) immaturity (usually prematurity); (*b*) birth trauma (especially intracranial hemorrhage); (*c*) respiratory difficulties arising during or immediately after birth; (*d*) infective and toxic conditions, and (*e*) congenital malformations.

6. (*a*) To give some idea of the neonatal mortality rates per thousand live births in different countries, the following figures are cited and the year to which the figure refers is given in parentheses. (By neonatal mortality is meant deaths during the first month of life):

Adelaide	(1936)	20
Holland	(1938)	21
Greater London	(1925)	26
Greater London	(1937)	24
England	(1938)	26
Chicago	(1925)	37
Chicago	(1937)	25
Scotland	(1938)	35
Glasgow	(1937)	43

(*b*) In order to give some idea of the total numbers of deaths involved, the following facts may be of interest:

	Total Number
Neonatal deaths in England and Wales each year	about 18,000
Stillbirths in England and Wales each year	about 25,000
Neonatal deaths in the United States of America each year	about 70,000
Stillbirths in the United States of America each year	about 72,000

7. Immaturity accounts for about 50 per cent of neonatal deaths and about 50 per cent of stillbirths. In many cases it is the primary cause of death; in others it constitutes a strong predisposing cause, because immature babies do not tolerate birth trauma and infections as well as mature babies; their respiratory transition is hazardous and they are particularly susceptible to lack of specialized nursing care. Those who survive are prone to acquire anemia, rickets and malnutrition, especially in the less favored classes.

The prevention of immaturity is a problem of major importance, and it is recommended that new efforts be made to solve it.

The treatment of immaturity requires special pediatric care supported by skilled nursing (a specially trained staff) in suitably equipped units; there is evidence that the usual death rate, of about 50 per cent, can be reduced in this way to less than 20 per cent. The chief aims of treatment are:

(*a*) Maintenance of steady temperature and prevention of dehydration by special heating appliances or conditioned air.

(*b*) Correct feeding (high calory feedings and liberal allowance of fluids), gavage often being necessary.

(*c*) Skilled nursing by a specially trained staff.

(*d*) Isolation from all possible sources of infection by provision of special isolation nurseries.

A premature infants' station or unit should be set up in every maternity hospital and in all important children's hospitals. Such stations should be in charge of pediatricians possessing experience in neonatal

care. Their value would not be limited to the care of the patients; they would be important teaching centers for undergraduates, postgraduates, midwives, children's nurses and health visitors.

8. With regard to birth trauma, it is obvious that attention should be centered mainly on prevention, which is a problem for obstetricians, general practitioners, physicians in charge of antepartum clinics and midwives in private practice. Pediatricians can assist by supporting all measures designed to secure first class obstetric practice.

9. The incidence of asphyxia neonatorum could probably be reduced by (*a*) securing a higher standard of antepartum care and (*b*) consulting with obstetricians and physiologists in order to reach conclusions on such points as (*1*) the use of analgesics and sedatives and (*2*) details of "first aid" care of the infant, including methods of resuscitation.

We desire to call attention to the lax use of the term "asphyxia neonatorum" on death certificates. There is little doubt that in many instances birth trauma, neonatal pneumonia and other conditions giving rise to (secondary) asphyxia masquerade under the title. A solution is difficult to see, but it is recommended that the attention of the Registrar General be called to the point. The importance of postmortem examinations in cases of this type is emphasized.

10. Members of both the medical and the nursing profession are still sadly ignorant about the prevalence and danger of neonatal infections, and there can be no efficient prophylaxis until this shortcoming is removed. The dangers are particularly great in institutions. Newborn infants should not be herded together, and this is especially true of newly born babies who are particularly prone to infections, e. g. premature infants, weak infants and infants with birth trauma or congenital malformations. These should be nursed under the direction of an expert pediatrician in a special unit, preferably designed on the cubicle system, and should be tended by a specially trained nursing staff employing modern methods of prophylaxis, including the use of gowns, masks, etc. There should be a basin for washing the hands in each cubicle. Nurses responsible for changing the babies should not prepare or give the food. A modern sterilizing apparatus should be used to disinfect napkins. A milk kitchen is required, not only to insure that artificial foods are prepared accurately and bottles and other equipment are thoroughly sterilized but to enable the nurses to receive adequate instruction in this important branch of the work, which should be supervised by a trained dietitian working under the control of a pediatrician. Breast milk is especially necessary for babies with infectious conditions (see paragraph 12), and the diets of the mothers require particular supervision (see paragraph 13).

11. In the present state of knowledge it is not possible to prevent congenital malformations; further research is necessary, particularly in regard to the possible influence of therapeutic agents, e. g. roentgen rays and radium.

12. An adequate and continuing supply of breast milk should be available for every infant, and particularly for immature, weak, birth-damaged and ill babies. It is a tragedy that many infants are given artificial feedings on the advice of doctors and nurses without sufficient justification. This fact provides a strong case for better and more vigorous instruction.

Not infrequently the supply of breast milk fails when the mother enters on her home duties again. Planning and supervision by the family doctor or home visitor or postpartum clinic would frequently prevent this failure, particularly if the mother's diet were to receive careful attention (see paragraph 13) and if she were able to take sufficient rest. Too speedy a return to strenuous household duties, such as washing, cooking and cleaning, results in tiredness, worry and failing health (especially anemia); it is not surprising that breast feeding often fails under these conditions. The psychologic aspects of breast feeding, which frequently breaks down because the mother is overanxious, lacking in confidence or worried, require careful consideration and should be stressed in the course of instruction given to medical students and nurses.

Banks or pools of breast milk, set up in maternity hospitals or other suitable centers, would be of great value to the surrounding district and should not be difficult to maintain; the blood banks started in recent years under the stimulus of war conditions have shown what can be done by concerted and vigorous effort.

13. The health of a newly born baby is greatly influenced by the state of the mother's health during the antepartum period. Diet, hygiene, attention to minor ailments (e. g. dental caries and secondary anemia) and freedom from worry are some of the subjects which need consideration by the family physician or the antepartum clinic. Only diet, to which much attention has been directed of late, will be mentioned here. There is evidence that satisfactory dieting during pregnancy diminishes the incidence of stillbirths, promotes the general well-being of newborn infants and improves the mother's capacity to provide breast milk. For the poorer classes it should be possible to insure that every pregnant woman receives a well balanced diet of some 2,500 calories with sufficient vitamins and minerals each day for the three months before confinement and throughout the period of lactation. In most districts these meals could be taken in the home, but in the poorer ones it might be more suitable for one meal of roughly 900 calories to be provided each day at a communal feeding center.

14. The subcommittee makes the following general recommendations:

(*a*) A committee composed of pediatricians, obstetricians and public health experts (with power to co-opt other specialists as necessary) should be set up to discuss all aspects of neonatal mortality and morbidity and to direct the further investigations which are necessary. The most important of their tasks would be to consider: (*i*) The health of pregnant women. (*ii*) The relative advantages of domiciliary and institutional confinement. (*iii*) Breast feeding. (*iv*) Prevention of immaturity. (*v*) Prevention of maternal and neonatal infections. (*vi*) Birth injuries. (*vii*) Respiratory difficulties at birth. This committee should be empowered to advise the Minister of Health in order that effective action may be taken.

(*b*) Undergraduates, postgraduates, midwives, children's nurses and health visitors are all in need of more tuition on neonatal health and disease. The central Midwives' Board should include at least one pediatrician, and the final examination should include questions on neonatal conditions set by a pediatrician, as is the custom in Northern Ireland.

(*c*) Each maternity hospital and most of the larger children's hospitals should have a properly equipped and efficiently staffed neonatal unit. These units would form part of the department of pediatrics in the region, and junior pediatricians would thus have better opportunities for clinical experience with children of the particular age period. The head nurses and senior nurses working in neonatal units should be qualified both as midwives and as children's nurses, and their salaries should be raised accordingly.

(*d*) It is hoped that the setting up of such a committee would insure close cooperation between the Ministry of Health and local health authorities, on the one hand, and pediatricians, on the other, which is essential for the efficient handling of the problem.

(*e*) Uniform standards for statistical returns from maternity hospitals and maternity nursing homes should be secured, and there should be a more general adoption of exact standards of immaturity or prematurity and careful and accurate returns of stillbirths.

PROF. CHARLES MCNEIL, Chairman
NORMAN B. CAPON, Secretary
W. R. F. COLLIS
S. G. GRAHAM
ALAN MONCRIEFF

September 1942.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

DEPENDENCE OF FETAL GROWTH AND STORAGE OF CALCIUM AND PHOSPHORUS ON THE PARATHYROID FUNCTION AND DIET OF PREGNANT RATS. M. BODANSKY and VIRGINIA B. DUFF, J. Nutrition **21**:25 (July) 1941.

Bodansky and Duff concluded that in rats the maintenance of suitable concentrations of calcium and phosphorus in the maternal blood was necessary for the development and storage of calcium and phosphorus in the fetus. In rats with intact parathyroids, the fetal growth and the storage of calcium and phosphorus were independent of the maternal intake of these elements. However, with an overabundance of calcium (an abnormally high calcium: phosphorus ratio) a definite impairment of the deposition of bone salts was noted in the embryo.

FREDEEN, Kansas City, Mo.

MAGNESIUM BALANCE STUDIES WITH INFANTS. CARROLL F. SHUKERS, ELIZABETH M. KNOTT and FREDERIC W. SCHLUTZ, J. Nutrition **21**:53 (July) 1941.

Shukers, Knott and Schlutz noted that a definite positive magnesium balance was maintained in infants from 2 to 6 months of age when they were given diets containing 10 to 20 mg. per kilogram of body weight per day. With the intake more than 20 mg. per kilogram per day, the retentions were of greater magnitude. Slightly better retentions were found with honey than with corn sirup as the carbohydrate added to the formula.

FREDEEN, Kansas City, Mo.

NUTRITIVE PROPERTIES OF STEAM-RENDERED LARD AND HYDROGENATED COTTONSEED OIL. RALPH HOAGLAND and GEORGE G. SNIDER, J. Nutrition **21**:65 (July) 1941.

Hoagland and Snider determined from their experiments with young male albino rats that steam-rendered lard was superior to hydrogenated cottonseed oil for growth-promoting properties and digestibility.

FREDEEN, Kansas City, Mo.

THE EFFECT OF DIETARY CALCIUM AND PHOSPHORUS ON THE ASSIMILATION OF DIETARY FLUORINE. MARGARET LAWRENZ and H. H. MITCHELL, J. Nutrition **21**:91 (July) 1941.

On the basis of experiments in which they increased the concentration of calcium in the diets of rats above certain minimum levels, Lawrenz and Mitchell concluded that there is a definite protection against the deleterious effects of dietary fluorine, especially in the teeth and soft tissues. This protection presumably is due to an impairment in the assimilation of fluorine.

FREDEEN, Kansas City, Mo.

THE EFFECT OF CERTAIN FATS AND UNSATURATED FATTY ACIDS UPON THE UTILIZATION OF CAROTENE. W. C. SHERMAN, J. Nutrition **22**:153 (Aug.) 1941.

W. C. Sherman fed a low fat diet and studied the effect of various natural oils and unsaturated fatty acids on the growth response of vitamin A–deficient rats to carotene. Soybean oil gave the best growth, while butterfat and coconut

oil had no appreciable effect. A beneficial effect was noted with cottonseed oil, linseed oil, wheat germ oil and corn oil. In feeding methyl linolate and methyl linolenate with low levels of carotene, Sherman reports an antagonistic action, characterized by a retarded growth rate and an incomplete cure of ophthalmia. However, with sufficient carotene fed with methyl linolate, a definite stimulation of growth was noted. A possible explanation for this antagonism was that the unsaturated fatty acids interfered with some phase of the metabolism of carotene or vitamin A, since the harmful effect of methyl linolate was largely overcome by feeding the two materials a few hours apart. From his analyses of carotene in the feces of the rats, Sherman stated that the differences in growth response to various oils and methyl linolate were not due to the differences in the effect of the oils on absorption of carotene.

FREDEEN, Kansas City, Mo.

STUDIES ON THE GROWTH AND DEVELOPMENT OF MALE CHILDREN RECEIVING EVAPORATED MILK: I. THE EFFECT OF VARIOUS VITAMIN SUPPLEMENTS ON GROWTH IN LENGTH AND INCIDENCE OF RICKETS DURING THE FIRST TWO YEARS OF LIFE. TERESA FOLIN RHOADS, MILTON RAPOPORT, RUTH KENNEDY and JOSEPH STOKES JR., J. Pediat. **19**:169 (Aug.) 1941.

Longitudinal observations were made of 233 male infants receiving diets containing evaporated milk as the sole source of milk from an average initial age of 6 weeks until the age of 2 years. The infants were divided into four groups according to vitamin supplements. Group I received irradiated evaporated milk; group II, nonirradiated evaporated milk plus cod liver oil; group III, irradiated evaporated milk plus carotene, and group IV, irradiated evaporated milk plus carotene and yeast. The average growth in length of all groups was better than would have been expected according to the Kornfeld standards of normal growth of boys, and there was no significant difference in length between any of the groups at 3 months, 1 year or 2 years. White children receiving 1,500 units of vitamin D in the form of cod liver oil between the ages of 3 months and 2 years increased in length by a suggestively, although not clearly significantly, greater amount than the children receiving 110 units of vitamin D in irradiated evaporated milk without added vitamins A and B. Negro children receiving cod liver oil increased in length a significantly greater amount than those receiving irradiated evaporated milk. Addition of 2,250 units of vitamin A in the form of carotene produced no significant effect on rate of growth in length of either the white or the Negro children. White children receiving carotene and approximately 250 units of vitamin B_1 and B_2 in powdered brewers' yeast between the ages of 3 and 24 months increased in length by a suggestively, although not clearly significantly, greater amount than the children on the same milk not receiving these vitamin supplements. For the Negro children, addition of yeast produced no significant increase in length. The incidence of roentgenographic rickets was practically the same at both levels of vitamin D intake (110 and 1,500 U. S. P. units daily). The various vitamin supplements had no influence on the incidence or severity of infections of the upper part of the respiratory tract.

RAUH, Cincinnati [From the Authors' Summary].

INTAKE OF AMINO ACIDS BY BREAST MILK FED INFANTS AND AMINO ACID COMPOSITION OF COW'S MILK AND HUMAN MILK. ELIOT F. BEACH, SAMUEL S. BERNSTEIN and ICIE G. MACY, J. Pediat. **19**:190 (Aug.) 1941.

Records of 3 infant girls' growth and nitrogen intake from their respective mother's milk provide data on the relations between gain in body weight, volume intake of milk, concentration of protein in human milk and estimated deposition of protein in body tissue. The amino acid intakes from breast milk protein by 2 normal, healthy infant girls during the first five months of life and for a third infant girl during her fourth and fifth months of life have been estimated from

amino acid analyses of human milk proteins. During their first five months, 2 infants of similar birth weight gained 3,260 and 3,220 Gm. of body weight, respectively, from 116.5 and 115.2 liters of their mothers' breast milk, containing 1,114 and 1,209 Gm. of protein. By Rubner's estimate of 30 Gm. of nitrogen per kilogram of body tissue, 611 and 604 Gm. of protein, respectively, were deposited in the infants' bodies, or approximately one half of the protein intake. The third infant, who weighed approximately 800 Gm. less at birth, demonstrated equally satisfactory gains in body weight on less milk of greater protein concentration. Calculated from analyses of mature human milk, these 2 infants' intakes of seven amino acids during the period from the second through the fifth month of life were, respectively, 13 and 15 Gm. of histidine, 42 and 50 Gm. of arginine, 52 and 62 Gm. of lysine, 52 and 62 Gm. of tyrosine, 20 and 23 Gm. of tryptophan, 21 and 25 Gm. of cystine and 19 and 23 Gm. of methionine. A comparison has been made of the composition of cow's milk and of human milk proteins with respect to seven amino acids, histidine, arginine, lysine, tyrosine, tryptophan, cystine and methionine. Gram for gram of protein, the two milks are nearly equivalent in histidine, arginine, lysine, tyrosine, tryptophan and organic sulfur; however, the organic sulfur in human milk protein is quite evenly divided between cystine and methionine, while in cow's milk protein the sulfur is largely in the form of methionine. A possible relation between this difference in sulfur distribution and the relative nutritive value of the milks of the two species is discussed.

RAUH, Cincinnati [Authors' Summary].

SOME OBSERVATIONS ON CALCIUM REQUIREMENT STANDARDS. J. P. MCGOWAN, Edinburgh M. J. **48**:494 (July) 1941.

The author quotes Cathcart's recent statement that "our knowledge of calcium needs is strikingly elementary." The quantitative standards which have been most consulted are those presented by Leitch (1936 to 1938), Sherman (1920), and Mitchell Hermann and associates (1939). Difficulties occur in interpretation, because there is much variation in the excretion of calcium among individuals and at different periods. The author believes that there would be an advantage in such measures as the addition of calcium to bread, though there is no guide as to how much should be used. Calcium carbonate is the cheapest available form of calcium, and in animals it is found to be of great advantage, provided vitamin D is supplied at the same time for its effect on absorption and metabolism. McGowan believes that it is not necessary for human beings to observe meticulous care in providing an exact amount but thinks attention should be paid to the quality of the lime preparation and to the supply of vitamin D.

NEFF, Kansas City, Mo.

DIET IN THE SECOND AND THIRD PERIODS OF INFANCY. EUGENIO TOUSSAINT ARAGON, Rev. mex. de pediat. **11**:1 (Jan.) 1941.

It is necessary to bestow the same attention on the diet of the second and third periods of infancy as on that of the nursing period. The diet must be quantitatively sufficient and of proper quality.

The protein should include both animal and vegetable protein. Milk should be limited to 500 cc. in twenty-four hours. Dextrose should be given in amounts of 7 to 10 Gm. per kilogram of body weight. Fats are given in amounts of 3 Gm. per kilogram of body weight, animal fats preferred. A physiologic amount of mineral salts, found in meats and vegetables, should be taken. Vitamins should be supplied, in the food when possible. Plenty of water should be given.

Failure to carry out the preceding suggestions will cause a break in the equilibrium of the regimen which will injure the child. This injury is not violent but gradual. It is not the economic factor but ignorance which usually causes defi-

ciencies in diet. The physician should insist on an adequate diet, including food of every kind. A daily schedule for the kinds as well as the quantities of food should be followed. It is clear that these notes are not the ultimate word in diet, as there are variations and new studies each year. GIFFEN, Toledo, Ohio.

SKIM MILK ACIDIFIED WITH LACTIC OR CITRIC ACID AS ADJUVANT TO BUTTERMILK. HANS SCHEIDEGGER, Ann. pædiat. **157**:101, 1941.

1. The preparation of acidified skimmed milk by addition of lactic or citric acid to fresh skimmed milk is described. A desirable fat content, of 1 or 2 per cent, is attainable by mixing skimmed milk with whole milk. The acidified skimmed milk can be used for making Finkelstein's protein milk by adding rennin curds.

2. Rearing immature infants by giving acidified milk in addition to breast milk was successful. Thirty-eight immature infants so fed had six times fewer dyspeptic disturbances than 39 immature infants who had dilution formulas in addition to breast milk. In 5 cases dyspepsia of an immature infant was cured by giving acidified skimmed milk. The increase of body weight was much better than with dilution formulas. No error occurred by increased hydration.

3. The results of treatment of nutritional disturbances with acidified skimmed milk were compared with those of treatment with acidified whole milk. In 116 cases of each series there were 5 attacks of intercurrent diarrhea with acidified skimmed milk and 37 with acidified whole milk. Vomiting also occurred less often with acidified skimmed milk.

4. The weight curves showed a better success of the infants with acidified skimmed milk, even if the first rise, caused possibly by augmented hydration, was disregarded.

5. For the treatment of acute and chronic nutritional disturbances acidified skimmed milk is superior to acidified whole milk. For healthy infants Scheidegger does not recommend this method.

6. The preparation is very simple and cheap. AUTHOR'S SUMMARY.

THE DETERMINATION OF SOYBEAN MILK USED AS AN ADULTERANT IN COW'S MILK. F. LIEBENTHAL and W. H. ADOLPH, Chinese M. J. **60**:174 (Aug.) 1941.

Vegetable milk made from soybeans ground with water has been added to cow's milk as an adulterant. Liebenthal and Adolph describe a test to determine the amount of soybean nitrogen present. The method was found to be rapid and accurate to about 2 per cent in reckoning the percentage of soybean substance in the mixture. Sodium chloride solution is added to the milk, the resulting mixture is centrifuged for one-half hour and the determination of the nitrogen in the coagulum is measured by the semimicro method of Kjeldahl.

NEFF, Kansas City, Mo.

Vitamins; Avitaminoses

THE EFFECTS OF SODIUM DIPHENYL HYDANTOINATE (DILANTIN) ON THE BLOOD ASCORBIC ACID LEVEL IN GUINEA PIGS. MILES E. DRAKE, CHARLES M. GRUBER, VICTOR G. HAURY and E. ROSS HART, J. Pharmacol. & Exper. Therap. **72**:383 (Aug.) 1941.

There has been a discrepancy in the results of different workers on the effect of dilantin sodium on the ascorbic acid levels of the blood in human beings and in experimental animals. This point was investigated by Drake, Gruber, Haury and Hart on 36 young female guinea pigs maintained on a diet with liberal dosage of ascorbic acid. After control periods of normal levels of ascorbic

acid in the blood, 27 of the animals were given daily doses of dilantin sodium corresponding to the clinical therapeutic dosage for man.

The normal ascorbic acid level of the blood was maintained in the control animals, but the level fell in the course of three weeks to somewhat less than one half of the normal level in the group which had been given dilantin sodium. In the latter, however, the normal blood level was regained in two weeks.

PILCHER, Cleveland.

COMPARATIVE COSTS OF VITAMIN C IN FRESH AND COMMERCIALLY CANNED FRUIT AND VEGETABLE JUICES. ARTHUR D. HOLMES, MADELEINE G. PIGOTT and FRANCIS TRIPP, New England J. Med. **225**:68 (July 10) 1941.

The authors bought oranges, grapefruit and lemons in retail stores in Boston and its vicinity and analyzed the vitamin C content of the various juices purchased. Their results were then compared with those reported by other observers. In a similar manner, cans of tomato, orange, grapefruit, lemon and pineapple juices were purchased and analyzed and the data compared with reports of other observers.

The average amount of juices required to supply 50 mg. of ascorbic acid (vitamin C), arranged in ascending order, are as follows: 106 cc. of fresh grapefruit juice; 107 cc. of fresh lemon juice; 116 cc. of fresh orange juice; 125 cc. of canned orange juice; 151 cc. of canned lemon juice; 167 cc. of canned grapefruit juice; 368 cc. of canned tomato juice, and 568 cc. of canned pineapple juice.

The average cost of 50 mg. of ascorbic acid from the various sources under consideration was found to be 2.7 cents for canned orange juice, 3.1 cents for canned grapefruit juice, 3.7 cents for fresh orange juice, 4.6 cents for fresh grapefruit juice, 6.3 cents for canned tomato juice, 7.0 cents for fresh lemon juice, 8.6 cents for canned lemon juice and 13.0 cents for canned pineapple juice.

GENGENBACH, Denver.

THE PREVENTION OF BERI-BERI. LYDIA FEHILY, Chinese M. J. **60**:53 (July) 1941.

Fehily states that in parts of China where highly milled rice has been used beriberi among adults has been known for over forty-five centuries. At the present time infantile and adult beriberi is seldom seen among the poorer classes, who use chiefly maize or millet. It is a different story in the cities, such as Shanghai, where white rice and wheat flour of inferior quality are common. The recognition of the condition is aided by the pale and puffy faces of the adults; and, in addition to such characteristics, infants show flabbiness and emaciation, with a facial expression of suffering. The infantile death rate per thousand live births during the year 1939 was 141 in Peiping and 345 in Hongkong.

The problem of B avitaminosis is great in Hongkong, where preventive measures must be adjusted to the social, economic and climatic conditions in that colony. The chief cause of the high infant mortality there is infantile beriberi. Avitaminosis B begins in the pregnant mother and continues throughout life among the poor classes. It retards growth of the fetus and produces abortions or death during, or immediately after, delivery. In the first month an infant gets breast milk intoxication from beriberi of the mother, with which 18 per cent of infants brought into the Hongkong welfare station are affected. Maternal avitaminosis reduces the amount of mother's milk and causes its disappearance. Infants are most susceptible to secondary infections, and they lack recuperative power. After the period of infancy the children of Hongkong have a better outlook. There is great difficulty in getting the Chinese to use any other type of rice than white.

The author suggests that only unhusked rice be imported into Hongkong and that improvement be made in storing and milling methods. Alternate foods, such

as mixed maize and soybean flour, should be provided for the diet, and a vitamin B preparation should be available to all members of the poorer classes, especially to mothers and infants. NEFF, Kansas City, Mo.

Acute Infectious Diseases

ACCIDENTAL TRANSMISSION OF MALARIA. SYDNEY H. GURIAN, Arch. Pediat. **59**:525 (Aug.) 1941.

Gurian reports a case of accidental transmission of malaria.

ORR, Buffalo.

THE PROGRESS IN RHEUMATIC HEART DISEASE. JOHN P. KIETH, Canad. M. A. J. **45**:119 (Aug.) 1941.

Rheumatic heart disease is more common in school children of the low income group than in those of the well-to-do group by about 8 to 1.

The occurrence of rheumatic heart disease is influenced by the manifestations appearing in children. Heart disease develops in 99 per cent of children with nodules; in 80 per cent of those with arthritis, and in 15 per cent of those with chorea associated with other rheumatic manifestations.

Of children who have had rheumatic manifestations but no heart disease, 25 per cent subsequently acquire heart disease.

Seventy-five per cent of children with rheumatic heart disease have one or more recurrences of rheumatic infection in the five years following the first attack.

Four per cent of the children die in the first attack and 12 per cent within five years and 20 to 30 per cent within ten years of the onset.

Eighty per cent of the children with the disease are leading an ordinary life five years after the onset; 59 per cent, three to fifteen years after the onset.

There is evidence of a reduction of approximately 25 per cent in deaths from rheumatic heart disease in children and young adults in the last fifteen years.

MOORE, Omaha.

THE FORMOL-GEL TEST DURING RHEUMATIC FEVER OF CHILDHOOD: COMPARISON WITH THE SEDIMENTATION RATE AND THE WELTMANN REACTION. REUBEN I. KLEIN, SAMUEL A. LEVINSON and CHARLES K. STULIK, J. Pediat. **18**:337 (March) 1941.

In a study of the formol-gel test, the sedimentation rate and the Weltmann reaction during rheumatic fever of childhood, the formol-gel test was found to be the least sensitive index of the rheumatic state and the corrected sedimentation rate the most sensitive. [In the formol-gel test a drop of the patient's serum is placed on a glass slide and the slide is inverted over a watch glass containing solution of formaldehyde; a positive result consists of the serum's solidifying into a jelly.] The Weltmann reaction is intermediate in sensitivity but gives unique information in that it helps to indicate the pathologic state of the rheumatic process, whether exudative or proliferative. In severe rheumatic carditis, the sedimentation rate is usually rapid and the Weltmann reaction gives a shift to the left, but the reaction to a formol-gel test is frequently negative. The "formol-gel test" is of little value in the study of rheumatic fever of childhood, because positive results are frequently obtained in the absence of carditis and negative results are obtained when carditis is obviously present. A combined study of the corrected sedimentation rate and the Weltmann reaction in rheumatic fever, when correlated with clinical observations, is of value in determining the state of the rheumatic process.

RAUH, Cincinnati [AUTHORS' CONCLUSIONS].

THE MODE OF ACTION OF NEOPRONTOSIL [AZOSULFAMIDE] IN STREPTOCOCCUS INFECTIONS IN MICE. J. T. LITCHFIELD JR., H. J. WHITE and E. K. MARSHALL JR., J. Pharmocal. & Exper. Therap. **72**:291 (July) 1941.

Litchfield, White and Marshall draw conclusions as follows:

The therapeutic activity of azosulfamide (disodium 4-sulfamidophenyl-2′-azo-4′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate) has been compared to that of sulfanilamide in a streptococcic infection in mice. Essentially the same blood concentration time curve as is associated with sulfanilamide was obtained from both drugs by use of the drug-diet method of therapy. The results show that the entire therapeutic activity of azosulfamide depends on the sulfanilamide formed from it.

PILCHER, Cleveland.

THE CHANGING HEART MURMURS OF ACUTE RHEUMATISM. A. J. GLAZEBROOK and SCOTT THOMSON, Edinburgh M. J. **48**:669 (Oct.) 1941.

In acute rheumatism systolic murmurs may be produced by fever and lack of tone in the valve rings. The murmurs may disappear completely at the time of convalescence. The author reports 5 examples of this in adolescent boys, in 3 of whom evidences of mitral stenosis by physical signs were present within sixty days of the beginning of the illness; in the other 2 boys aortic incompetence was shown by the physical signs which came on within twenty days, lasted two months and seven months respectively and then disappeared. The author emphasizes the changing character of the murmurs in the individual subject.

NEFF, Kansas City, Mo.

ACUTE RHEUMATISM AND TRAUMA. A. J. GLAZEBROOK and SCOTT THOMSON, Edinburgh M. J. **48**:674 (Oct.) 1941.

This study concerns 11 adolescent boys in whom there was a well recognized role of trauma accompanying acute rheumatic fever. The traumatized joint was the first one affected in the sequel of rheumatic polyarthritis. The cases occurred among youths who were taking part in physical instruction and games in an institution. After the injury there was a return of pain and swelling in the joint which had been traumatized.

NEFF, Kansas City, Mo.

THE HEREDITARY TRANSMISSION OF THE RICKETTSIAE OF TICK-BITE FEVER THROUGH THE COMMON DOG-TICK, HAEMAPHYSALIS LEACHI. J. GEAR and B. DE MEILLON, South African M. J. **15**:389 (Oct. 11) 1941.

The authors describe experiments in which it was demonstrated that rickettsias of tick bite fever are transmitted through the egg of the common dog tick, Haemaphysalis leachi, to the succeeding generation and through the eggs of the second generation to the third generation. It was also shown that all stages of the tick, larva, nymph and adult, are infective. The virus does not kill the tick nor seem to have any deleterious effect on it in any of its stages. Of practical importance is the demonstration that the rickettsias of tick bite fever do not require the intervention of a mammalian host for their propagation. The tick may act as a reservoir which preserves the infection indefinitely and may infect human beings at any active stage of its life.

GONCE JR., Madison, Wis.

Chronic Infectious Diseases

ANTITUBERCULOUS PROPHYLAXIS. P. RICHARD, Union méd. du Canada **70**:752 (July) 1941.

Since tuberculosis is a contagious disease, the first step in prophylaxis is the isolation of persons with an open infection. The general health of the whole population must be raised and hygienic living conditions established. Bovine

tuberculosis must be eradicated. All milk should be pasteurized. Finally, all infants and all adults with negative reactions to tuberculin should receive BCG vaccine.

DAFFINEE, Boston.

STUDIES IN TUBERCULOSIS: II. THE RELATIVE INCIDENCE OF HUMAN AND BOVINE TYPES OF MYCOBACTERIUM TUBERCULOSIS IN HUMAN DISEASE IN VICTORIA. R. WEBSTER, M. J. Australia **2**:49 (July 19) 1941.

No instance of bovine tuberculosis infection occurred in 183 adult subjects with tuberculosis in a variety of clinical forms. All the cultures were obtained from extrapulmonary sources except for 14 from pleural exudates and 6 from sputum. Of 123 children, 11 were infected with Mycobacterium tuberculosis of bovine type—an incidence of bovine infection of 8.9 per cent. A similar investigation completed in 1932 showed a rate of bovine infection of 25.9 per cent. The present lowered incidence is correlated with a striking reduction in the number of reactors to tuberculin in herds supplying milk for distribution in the Melbourne metropolitan area. The bovine type of infection was not encountered outside the group of tissues comprised by the tonsils and the cervical and mesenteric glands. It is particularly noteworthy that in every instance the organism recovered from tuberculous bones and joints of 20 children and 45 adults was of the human type.

GONCE, Madison, Wis.

THE INCIDENCE OF CONGENITAL SYPHILIS AND ITS PROPHYLAXIS. MARIO RAMOS, Rev. méd. munic. **2**:507 (Oct.) 1941.

This is a rather interesting article on the problems of congenital syphilis in Rio de Janeiro. In 1933, of 3,000 infants to 2 years of age 4 per cent showed active syphilis, 1 per cent latent and 2 per cent dystrophic. Of 2,000 preschool children 2 to 6 years old, 1 per cent had active syphilis, 3 per cent latent and 14.6 per cent dystrophic. Early diagnosis by means of roentgenograms is advocated. Since that time active treatment of mothers and children has been carried out.

SANFORD, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

THE VALUE OF STERNAL MARROW ASPIRATION AS A METHOD OF BONE MARROW BIOPSY. ERNEST H. FALCONER and MAURICE E. LEONARD, Ann. Int. Med. **15**:446 (Sept.) 1941.

The authors found that the usual method of obtaining bone marrow for biopsy by means of aspiration through a spinal puncture needle is satisfactory.

READING, Galveston, Tex.

IDIOPATHIC CARDIAC ENLARGEMENT OCCURRING IN INFANTS AND CHILDREN. J. MARSHALL NEELY, Ann. Int. Med. **15**:727 (Oct.) 1941.

The author reports the cases of 3 children varying in age from 25 days to 3 years who before death revealed cardiac hypertrophy without demonstrable cause. At necropsy in each instance chronic interstitial pneumonitis was found.

READING, Galveston, Tex.

STUDIES IN EXPERIMENTAL HYPERTENSION. HARRY GOLDBLATT, JOSEPH R. KOHN and HARVEY A. LEWIS, Arch. Surg. **13**:327 (Sept.) 1941.

Studies on experimental hypertension due to renal ischemia showed that constriction of the main artery of only one kidney in a dog or a monkey was sufficient to cause elevation of the blood pressure. In subsequent studies by the authors it was also shown that this elevation does not usually persist indefinitely

unless the other kidney is removed or unless the main artery of the other kidney is also constricted. In most of the experimental animals with unilateral renal ischemia, the blood pressure returns to the preoperative level in six weeks or less. The return of the blood pressure to normal is thought to be due either to the development of considerable accessory circulation to the ischemic kidney or to the compensating or inhibiting effect of the contralateral normal kidney. The practical application of these experiments in human subjects, the authors point out, indicates that the excision of the kidney should be undertaken for the main purpose of removing the diseased organ rather than for possible cure of the hypertension.

KAISER, Rochester, N. Y.

AURICULAR PAROXYSMAL TACHYCARDIA IN INFANCY. HAROLD N. SEGALL and ALTON GOLDBLOOM, Canad. M. A. J. **45**:64 (July) 1941.

Segall and Goldbloom report on a case of auricular paroxysmal tachycardia in an infant 18 months of age.

When the child was 3 months of age, the mother had noted a sudden attack of blueness, heavy breathing and a rapid pulse. This lasted about fifteen minutes. Several similar attacks occurred in the next five months.

The electrocardiogram demonstrated an arrhythmia due to an auricular paroxysmal tachycardia.

Twenty cases of this type of arrhythmia in infants under 1 year of age have been reported.

The literature is briefly reviewed.

MOORE, Omaha.

INTERSTITIAL MYOCARDITIS IN MICE AND RATS PRODUCED BY NEOPRONTOSIL, SULFANILAMIDE, SODIUM SULFAPYRIDINE AND SODIUM SULFATHIAZOLE. A. JAMES FRENCH, Proc. Soc. Exper. Biol. & Med. **48**:1 (Oct.) 1941.

Routine examination of human autopsy material disclosed interstitial myocarditis in a number of instances when a sulfonamide compound had been given. This prompted the author to administer neoprontosil and later other sulfonamide compounds to rats, mice and rabbits, and in a large portion of the animals interstitial cellular infiltration of the myocardium was found. Only in rabbits did the control animals show evidence of a "spontaneous" myocarditis. The interstitial myocarditis in the experimental animals was in part eosinophilic and appeared histologically similar to that observed in the hearts of human subjects dying after the administration of drugs of the sulfonamide group.

HANSEN, Minneapolis.

CORONARY CALCIFICATION AND THROMBOSIS IN AN INFANT. S. VAN CREVELD, Ann. pædiat. **157**:84, 1941.

Van Creveld describes a case of coronary calcification and thrombosis in a girl of 7 weeks with peculiar swelling and necrosis of the capillary endothelium of the glomeruli of the kidney. The hypothesis was assumed that the coronary deviations were related to the regular use of drugs by the allergic mother, giving rise to a localized hyperergic reaction.

AUTHOR'S SUMMARY.

Diseases of Nose, Throat and Ear

THE ACUTELY INVOLVED MASTOID (WITHOUT COMPLICATIONS) BEFORE AND AFTER OPERATION: A CLINICAL AND ROENTGENOLOGIC STUDY. CHARLES W. BARKHORN, Arch. Otolaryng. **34**:69 (July) 1941.

Four illustrative cases are reported. Barkhorn advocates that a definite plan be adopted and followed as routinely as possible in all cases of mastoid infection,

with avoidance of too early surgical intervention and more reliance on preoperative roentgenograms and clinical procedures. The relative importance of postoperative roentgenograms is also discussed.

GREENWOOD, Chicago.

SINUSITIS AND STAPHYLOCOCCUS AUREUS BACTEREMIA: RECOVERY. HENRY H. BEINFIELD, Arch. Otolaryng. **34**:164 (July) 1941.

A case of sinusitis and bacteremia due to Staphylococcus aureus is reported by Beinfield.

Sulfanilamide therapy was instituted and reduced the number of staphylococcic colonies from 25 to 2 per cubic centimeter in three days.

GREENWOOD, Chicago.

CONGENITAL CYST OF THE LARYNX. S. F. CRYNES and S. C. YINGER, Arch. Otolaryng. **34**:170 (July) 1941.

Crynes and Yinger present the case of a congenital laryngeal cyst which was successfully removed. Complete cure resulted.

The unusual feature of a stratified squamous epithelial lining with numerous hyperplastic lymph follicles within its wall was encountered.

GREENWOOD, Chicago.

ABERRANT SALIVARY GLAND IN TONSILLAR FOSSA. WILLIAM J. HITSCHLER and THOMAS A. COPE JR., Arch. Otolaryng. **34**:174 (July) 1941.

Hitschler and Cope report a case of an aberrant salivary gland in the tonsillar fossa. Only a few cases of this anomaly have appeared in the literature.

GREENWOOD, Chicago.

ABSCESS OF THE MANDIBULAR FOSSA SECONDARY TO OTITIS MEDIA. HAROLD I. LILLIE and KINSEY M. SIMONTON, Arch. Otolaryng. **34**:485 (Sept.) 1941.

Lillie and Simonton present 2 cases in which the symptoms and signs of abscess in the mandibular fossa were definite and identical. Evidence in these cases led to the conclusion that extension of infection from the middle ear to the mandibular fossa takes place through the glaserian fissure. Treatment by direct primary surgical exposure of the mandibular fossa rather than by drainage of secondary extensions of the abscess is discussed.

GREENWOOD, Chicago.

PLASTIC CORRECTION OF PROTRUDING EARS IN CHILDREN. HAMILTON BAXTER, Canad. M. A. J. **45**:217 (Sept.) 1941.

Since abnormally prominent auricles are almost invariably due to a congenital anomaly of structure, surgical correction is necessary to remedy the condition.

With the improvement of the patient's appearance the mental complex resulting from the abnormality clears up.

The surgical technic is discussed and illustrated.

MOORE, Omaha.

Diseases of Lungs, Pleura and Mediastinum

MASS RADIOGRAPHY OF THE CHEST. B. P. A. STUART, M. J. Australia **2**:27 (July 12) 1941.

For carrying out mass roentgenography of the chest, four methods are available: (1) direct roentgenography on a large film, (2) fluoroscopy, (3) fluorography by means of 5 by 4 inch (12.5 by 10 cm.) roentgen films and (4) fluorography by means of 35 mm. roll films. Of these methods, the last mentioned is the only one

fulfilling all requirements for mass roentgenography. Ultimately, this will be the chief weapon in the campaign against tuberculosis, and undoubtedly it is the greatest single contribution roentgenology has ever made toward improving and safeguarding the health of a nation.

GONCE, Madison, Wis.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

VINCENT'S ULCEROMEMBRANOUS GINGIVOSTOMATITIS. JOSEPH SCHWARTZMAN and LEO GROSSMAN, Arch. Pediat. **58**:515 (Aug.) 1941.

Schwartzman and Grossman review 33 cases of Vincent's ulceromembranous gingivostomatitis. Attempts at direct transmission were unsuccessful in 25 cases, tending to disprove the communicability of the disease by contact.

The authors felt that favorable results were obtained when nicotinic acid (niacin) was employed in treatment. They expressed the belief that the disease is primarily due to a deficiency of nicotinic acid and only when this condition exists can the organisms involved become active invaders.

ORR, Buffalo.

TREATMENT OF INTUSSUSCEPTION. JAY IRELAND, Arch. Surg. **43**:418 (Sept.) 1941.

Ireland analyzed the cases of 133 patients admitted to one hospital with the diagnosis of intussusception over a period of twenty years. During the years 1920 to 1930, 54 patients were treated surgically, with an operative mortality of 41 per cent. During the next ten years, 79 patients were similarly treated, with a mortality of 22 per cent. Reduction was accomplished with enemas in 11 patients, though it was attempted in 64 of the 133 patients. In 2 patients with an irreducible intussusception, glycerin was injected between the intussuscipiens and the intussusceptum and successful reduction was accomplished.

KAISER, Rochester, N. Y.

SUCCINYL SULFATHIAZOLE, A NEW BACTERIOSTATIC AGENT LOCALLY ACTIVE IN THE GASTROINTESTINAL TRACT. EDGAR J. POTH and F. LOUIS KNOTTS, Proc. Soc. Exper. Biol. & Med. **48**:129 (Oct.) 1941.

Succinyl sulfathiazole administered by mouth to dogs greatly reduced the content of the coliform organisms in the bowel, and at the same time the feces became semifluid and practically odorless. The same drug was given to 40 human subjects with essentially the same results, and at the same time no toxic reactions occurred. The activity of this drug is largely due to its local effect on the contents of the gastrointestinal tract.

HANSEN, Minneapolis.

STUDIES OF THE ACUTE DIARRHEAL DISEASES: V. AN OUTBREAK DUE TO SALMONELLA TYPHI MURIUM. W. E. MOSHER, Pub. Health Rep. **56**:2415 (Dec. 19) 1941.

An outbreak of acute diarrheal diseases occurred in an institution, and 238 inmates were affected, with 1 death. Salmonella typhi murium was isolated from the stools of 36.1 per cent of the inmates with symptoms. The medium was turkey or its dressing. One patient carried the organism for eighteen weeks.

SANFORD, Chicago.

EXOMPHALOS. LAMBERT ROGERS, Brit. J. Surg. **29**:37 (July) 1941.

During the forenoon of Jan. 5, 1935, a midwife, bearing in her arms a newly born child, was announced at the entrance to the theater where the author was carrying out a morning's list of operations. The infant was found to have the abdominal viscera lying on the abdominal wall, covered only by a transparent membrane resembling Wharton jelly. The child was taken into the operating theater at once, and without anesthesia the intestines and liver were replaced through the gap in the abdominal wall. Although considerable handling of the

viscera was necessary for this replacement, the child was not perceptibly disturbed and made an uninterrupted recovery. A photograph shows the child, now 4 years old, with some bulging of the ventral scar. KEITH, Toronto, Canada.

GIANT ANGIOMA OF THE MESENTERY. A. C. SALAZAR, R. BUIGAS, E. HECHAVARRIA Y SRTA and G. GODINEZ, San. y benefic. munic. **1**:109 (Oct.-Dec.) 1941.

The authors report on a cavernous angioma of the mesentery in a 9 month old child. It was removed surgically with excellent results. Numerous photographs are shown of the tumor, the child and the operation. SANFORD, Chicago.

Nervous Diseases

SUBCORTICAL HEMATOMA: SURGICAL TREATMENT, WITH REPORT OF EIGHT CASES. COBB PILCHER, Arch. Neurol. & Psychiat. **46**:416 (Sept.) 1941.

The author reports the cases of 8 patients with subcortical hematoma who were operated on. One of these was a 5 year old boy and another a 16 year old boy. In these 2 patients the cause was trauma; in 5 cases the hemorrhage was spontaneous. The symptoms were those usually associated with hemorrhage: sudden or rapidly developing stupor and eventually coma with localizing signs. The hemorrhage is found by decompression and aspiration of the brain. Recovery was complete in the 2 boys and in 2 of the adults. BEVERLY, Chicago.

VASCULAR MALFORMATIONS AND VASCULAR TUMORS INVOLVING THE SPINAL CORD: A PATHOLOGIC STUDY OF FORTY-SIX CASES. OSCAR A. TURNER and JAMES W. KERNOHAN, Arch. Neurol. & Psychiat. **46**:444 (Sept.) 1941.

Between 7 and 9 per cent of both intramedullary and extramedullary tumors of the spinal cord are vascular. These angiomas, arteriovenous and venous, progress by enlargement of the individual vessels which go to make up the tumor mass. An inflammatory process may be part of the picture.

BEVERLY, Chicago.

CONGENITAL ABSENCE OF THE SEPTUM PELLUCIDUM: A CASE DIAGNOSED ENCEPHALOGRAPHICALLY AND ASSOCIATED WITH CONGENITAL AMAUROSIS. DAVID L. REEVES, Bull. John Hopkins Hosp. **69**:61 (July) 1941.

Encephalography of an infant of 7 months with congenital amaurosis revealed the characteristic features of congenital absence of the septum pellucidum. This case, the third reported since the first encephalographic description of the unusual anomaly in 1935 by Dyke and Davidoff, was so diagnosed at the earliest recorded age.

The medial confluence of the anterior lateral ventricles and normal posterior separation represent the main diagnostic features of the anteroposterior and posteroanterior views.

The differences between the encephalographic findings in agenesis of the corpus callosum and cysts of the septum pellucidum is discussed.

It is believed that as the encephalographic picture of the condition becomes appreciated, more of these cases will be described in the future.

AUTHOR'S SUMMARY.

SYDENHAM'S CHOREA: PRELIMINARY REPORT OF THREE CASES SUCCESSFULLY TREATED WITH VITAMIN B_6. JOSEPH SCHWARTZMAN, DAVID DRAGUTSKY and GEORGE ROOK, J. Pediat. **19**:201 (Aug.) 1941.

Three children, a girl aged 8½ years and 2 boys 10 and 11 years of age, suffering from chorea were treated with vitamin B_6 (pyridoxine). In 1 instance the drug was administered orally; in the other 2 cases, intravenously. The amount

of the drug required varied from 180 to 840 mg. Improvement was not noted until treatment had been carried on for several days, and the improvement was at first gradual, causing a diminution in the intensity of the involuntary movements and a feeling of general comfort and restfulness. In fact, subjective amelioration preceded objective improvement. However, once improvement began, the increment of amelioration was progressively increased and complete cessation of all symptoms followed fairly rapidly.

RAUH, Cincinnati.

DEMONSTRATION OF MYELOLYTIC SUBSTANCES IN DISSEMINATED SCLEROSIS. ARTHUR WEIL and GERT HEILBRUNN, Proc. Soc. Exper. Biol. & Med. **48**:233 (Oct.) 1941.

Extracts of urine of patients with disseminated sclerosis were found to have a pronounced myelolytic effect when incubated with spinal cords of rats. Seventy per cent of 165 patients with disseminated sclerosis showed this phenomenon, which was more pronounced during exacerbations of the disease. Sixty-five per cent of 43 patients with postencephalitic parkinsonism and 5 per cent of 83 patients with other diseases of the central nervous system showed the same phenomenon, whereas no effect on the myelin sheaths of spinal cords of rats occurred with extracts of urine of 9 patients with dementia paralytica and 25 normal control subjects.

HANSEN, Minneapolis.

THE REHABILITATION OF CEREBRAL PALSY. W. M. PHELPS, South. M. J. **34**:770 (July) 1941.

Phelps reports that cerebral palsy represents a major problem both from a public health and from a rehabilitation viewpoint, considering its frequency and distribution. The disease presents a multiple problem which involves not only a motor handicap but sensory phases, usually defects of the special senses of sight and hearing, which must also be treated. Mental deficiency is sometimes present, but this must be determined only after careful evaluation of all other handicaps.

Cerebral palsy is of one of three general motor types, namely, athetosis, spasticity and ataxia, and the treatment of these types varies widely. These conditions are not curable, but are capable of great improvement with thorough and adequate treatment and substitution methods. The aims to be attained in each case must be carefully worked out with regard to the legs for locomotion, the arms for self help, the speech organs and general appearance. Rehabilitation of the patient should be considered first. He should be freed from the care of another if possible, even though complete or economic rehabilitation should not prove possible.

SCHLUTZ, Chicago.

ACUTE HEMORRHAGIC LEUCOENCEPHALITIS: A PREVIOUSLY UNDEFINED ENTITY. E. W. HURST, M. J. Australia **2**:1 (July 5) 1941.

The name "acute hemorrhagic leukoencephalitis" is given by Hurst to an acute nervous disease characterized by severe damage to the walls of blood vessels, perivascular necroses, perivascular and focal demyelination, intense polymorphonuclear exudation and microglial reaction. When lesions are most severe, edema and hemorrhages are conspicuous. In the cerebrum the lesions are confined almost exclusively to the white matter. Clinically, the chief feature is a rapid or rather rapid abrogation of the higher cerebral functions in a previously healthy person; this is associated with headache, vomiting, slight pyrexia or leukocytosis. The lesions in 2 patients with this condition are compared with those in persons with purpura of the brain and with Baker's hemorrhagic encephalitis. Hurst suggests that acute hemorrhagic leukoencephalitis may represent a link between the demyelinating diseases on the one hand and some forms of hemorrhagic encephalitis on the other.

GONCE, Madison, Wis.

PATHOLOGIC CHANGES IN BRAINS OF EPILEPTIC PERSONS WHO DIED DURING STATUS EPILEPTICUS. OSORIO CESAR, Arq. Serv. assist. psicop. estad. São Paulo **6**:243 (Sept.-Dec.) 1941.

The brains of 3 young epileptic persons (15, 17 and 18 years of age) who died during status epilepticus were examined. There was no evidence of intercurrent disease in any of them. The most significant observation in all the brains was the presence of many rounded cavities of varying size throughout the cortex. These cavities were not surrounded by inflammatory changes or glial proliferation. Occasionally ganglion cells near the edges of these cystlike structures seemed to be thinned out, as though compressed. Here and there widely dilated perivascular spaces were seen. Acute, and more rarely chronic, degenerative changes of ganglion cells were noted, with various stages of chromatolysis and alteration in the Nissl substance. Spotty areas of *Ausfall* of cells were seen, with some disorganization of the architectonics of the cortex.

The cases reported are particularly significant because the patients were all young and died in status epilepticus, without evidence of concomitant disease. The author considers the disseminated cortical lacunas of diagnostic significance. The observations confirm the previous observations of Pupo. The anatomic changes indicate the existence of a disturbance of water regulation in the brain—an intracerebral hydrops.

SAVITSKY, New York [ARCH. NEUROL. & PSYCHIAT.].

ACTION OF FORMALDEHYDE ON THE NERVOUS SYSTEM. FLAMINO VIDAL and EUGENIO E. VONESCH, Rev. méd. latino-am. **26**:1105 (July) 1941.

In the study of necropsy material the effect of prolonged fixation in solution of formaldehyde is of interest. The changes formerly attributed to autolysis are now known to be due in some measure to the action of the fixing agent. The authors have studied brains of man and of lower animals that have been fixed in solution of formaldehyde. This agent has a rapid and prolonged disintegrating action on the phospholipids and extracts about 8 per cent of the solid substances.

DWYER, Kansas City, Mo.

GRIP MENINGITIS. HERBERT NATHHORST. Ann. pædiat. **157**: 93, 1941.

Nathhorst described 15 cases of meningitis caused by Bacillus influenzae in children. Six children were treated with sulfapyridine, of whom 2, aged 8 and 10 years respectively, were cured. Of the patients not treated with sulfapyridine, only 1 child, aged 3 years 6 months, was cured. With 1 exception all the patients who died were younger than 2 years. Age seems to be of great importance for the prognosis.

AUTHOR'S SUMMARY.

THE TREATMENT OF INFANTILE TETANY WITH DIHYDROTACHYSTEROL (A. T. 10). THERESA T. WOO, CHUAN FAN and FU-T'ANG CHU, Chinese M. J. **60**:99 (Aug.) 1941.

The earlier use of dihydrotachysterol in Germany for the treatment of hypoparathyroid tetany led these Chinese workers to try it in the tetany of infants. Five infants were treated during the spring of 1940. The calcium level of the serum was low in all subjects, and clinical symptoms were present. The infants at onset of symptoms were from 4 to 52 days old.

A prompt response came from the use of this drug in 4 cases. The dose of 1 to 1.5 cc. daily (of a 0.5 per cent solution) was given for one to four days.

NEFF, Kansas City, Mo.

Psychology and Psychiatry

THE HEREDITARY FACTOR IN MENTAL DEFICIENCY. A. T. HOPWOOD, C. C. KIRK and F. L. KEISER, Am. J. Psychiat. **98**:22 (July) 1941.

Hopwood, Kirk and Keiser studied thousands of records from institutions for the feebleminded and the state hospitals, as well as thousands of commitment papers. They excluded all instances of feeblemindedness in which there was an organic factor, such as cretinism or mongolism. In this manner, they obtained material on 1,765 families. In 821 families with evidence limited to one generation the authors found 1,880 siblings or cousins who were mentally defective, epileptic or insane. In 317 of the 827 families in which the evidence was confined to two generations, mental deficiency was found in the parents. There were 1,161 mentally defective children, and in the 827 families 2,334 persons were mentally defective, epileptic or insane. Furthermore, in 115 families in this group one or both parents and one or more children were mentally defective. Among 114 families which were studied for three generations there were 256 mentally defective persons. Hopwood, Kirk and Keiser point out the preponderance of morons and imbeciles over idiots (85:15 per cent). They conclude that it is safe to assume that in 50 per cent of their cases the conditions could be attributed to heredity.

FORSTER, Boston [ARCH. NEUROL. & PSYCHIAT.].

MEASURES WHICH CHARACTERIZE THE INDIVIDUAL DURING THE DEVELOPMENT OF BEHAVIOR IN EARLY LIFE. R. V. D. CAMPBELL and A. A. WEECH, Child Development **12**:217 (Sept.) 1941.

Longitudinal data on 40 infants, including 5 sets of unisexual twins, were analyzed statistically in order to assess the extent to which the individual is characterized by his development in such behaviors as creeping, sitting and walking. The reliability of the several measures in characterizing the individual was tested by two methods. In the first method the variability of each child in several activities was compared with the variability throughout the group. The second method depended on the relative position of twins in a scale of order of rank of the measures. Both methods led to identical conclusions. At birth the individual is rather poorly differentiated from the group. He is characterized somewhat better in terms of his rate of approach to average mature behavior. In terms of achievement itself he is more and more sharply differentiated up to an age of at least 150 days. It seems unlikely that scales of achievement in behavior can yield satisfactory appraisals of the individual under the age of 3 months. At later ages such scales can be expected to provide increasingly accurate means of assessing individual attainment.

AUTHORS' SUMMARY.

THE RELATION BETWEEN THE DEVELOPMENT OF BEHAVIOR AND THE PATTERN OF PHYSICAL GROWTH. A. A. WEECH and R. V. D. CAMPBELL, Child Development **12**:237 (Sept.) 1941.

The authors correlated quantitative measures of the development of 33 infants in such behaviors as sitting, creeping and walking with the body weights of the infants at 50 days and with the percentage increases in weight during the age period from 50 to 150 days. On the average infants who are heavy at 50 days show relatively small percentage gains and exhibit relatively rapid development in behavior. Infants who are small at 50 days show relatively large percentage gains and develop rather slowly in behavior.

AUTHORS' SUMMARY.

DEVELOPMENTAL CHANGES IN ATTITUDE AS ONE FACTOR DETERMINING ENERGY OUTPUT IN A MOTOR PERFORMANCE. VERA T. DAMMANN, Child Development **12**:241 (Sept.) 1941.

Three children were given daily practice in creeping up a slide clamped successively to stools of graded heights forming inclines of varying angles; time of

ascent was recorded by stopwatch. These data were collected for Weinbach's series of studies, "Physiological Phenomena Fitted to Growth Equations." Despite widely divergent temperamental makeup, all 3 children manifested the following developmental phases in change of attitude: (1) In the young infant just beginning to creep diffuse interest in the environment and short attention span influence motor performance adversely; (2) interest in specific object-lures enhances performance, but overstimulation by them may impede, and sometimes even block, performance; (3) the procedure becomes ordered into a definite *Gestalt*, and the performance is gone through almost compulsively, the child himself placing the lure at the top and then creeping up to retrieve it; (4) the "mechanism" has become a "drive" and satisfaction in performing the motor act makes for optimum proficiency; (5) performance is largely governed by mood and is good or poor according to whether the child is interested or bored. Since a major condition for optimum performance is cooperative attitude, experimental conditions were adapted to fit the changes in attitude.

AUTHOR'S SUMMARY.

SIZE DISCRIMINATION IN CHILDREN. LOUIS LONG, Child Development **12**:247 (Sept.) 1941.

The ability of young children to discriminate between stimuli varying in size was studied by means of a standard discrimination technic. The stimuli were circles, squares and rectangles. In one part of the experiment the paired stimuli were of the same geometric shape and of different sizes (e. g., large square and small square), whereas in another part the stimuli differed in shape as well as in size (e. g., large square and small circle). Ten of 12 subjects learned the initial discrimination. The number of trials taken to learn this discrimination varied from 5 to 437. The results indicate that the subjects were able to select the larger of two circles, two squares or two rectangles with about the same degree of accuracy. The children were also able to select the larger stimulus, even though the shapes of the two figures were not the same. For example, the child was able to select the larger of two squares just as readily as the larger of two circles; but selecting the larger of a square and circle is a more difficult task, as evidenced by the fact that more errors were made in this type of discrimination. The task of selecting the larger of two figures differing in shape was therefore more difficult than selecting the larger of two figures of the same shape.

AUTHOR'S SUMMARY.

CHILDREN'S REACTIONS TO MOVIE HORRORS AND RADIO CRIME. MARY I. PRESTON, J. Pediat. **19**:147 (Aug.) 1941.

Preston studied the reactions of 200 children from 6 to 16 years of age to movie and radio programs described as "bad" or "scary." The reactions of these children were compared with those of a group of 47 children who had escaped "bad" movies and radio. Preston found that addiction to movie horrors and radio crime was detrimental to the general health. In the group addicted to the "bad" movies and radio, nervousness was increased in amount (76 per cent as against 40 per cent in the nonaddicts) and in degree (52 per cent versus 4 per cent). Sleeping disturbances were four times more common among the addicts than among the control group. Fears were increased fivefold among the addicts. In the homes of high standard of child training, regardless of social, economic or intellectual standing, movie horrors and radio crimes were eliminated. In these homes other sources of recreation and social life had been provided for the children. Treatment of the addicts consisted in attempts to restrict the frequency of indulgence and to eliminate these movie and radio horrors and to substitute better recreational and social activities in the home.

RAUH, Cincinnati.

A CONGENITAL FORM OF AMAUROTIC FAMILY IDIOCY. R. M. NORMAN and N. WOOD, J. Neurol. & Psychiat. **4**:175 (July-Oct.) 1941.

Norman and Wood report an unusual form of lipidosis in an 18 day old female infant. The family history was inconclusive. The pregnancy and labor were normal, but a few days after birth the baby became "blue" and began regurgitating fluids immediately after feeding; she later died of bilateral renal hemorrhages. The essential postmortem observation was a microcephalic brain, weighing 87 Gm., with pachygyric convolutions and shallow sulci and a particularly small cerebellum. Histologically, the changes were characteristic of amaurotic family idiocy, consisting of widespread swelling of nerve cells and gliocytes, which were distended with lipid deposits. There was also microscopic evidence of lipid storage in the reticuloendothelial system of the spleen, lymph nodes, liver and adrenal glands. Besides the fetal time of onset and the extreme micrencephaly, the following histochemical features distinguish the condition in this case from Tay-Sachs disease: (*a*) The occurrence within the cerebral cortex and the Purkinje layer of the cerebellum of large, bizarre, spherical cells, occasionally binucleated and laden with lipids. These cells resembled atypical neurons, their modified structure probably being conditioned by the fetal onset of the lipidosis. (*b*) Insolubility of the lipid material in xylene or boiling chloroform, the substance thus chemically resembling the lipochrome material found in the juvenile form rather than the prelipids of Tay-Sachs disease. There was also absence of neutral fat, which is common in the latter disorder. (*c*) A heavy crystalline deposit of cholesterol esters throughout the white matter of the cerebrum and cerebellum. In addition, there were an unusually noticeable arrest in myelination and lack of production of fibrillary gliosis. This probably coincides with the fetal onset of the condition and thus may account for the extreme micrencephaly. The atrophy of the cerebellum is not uncommon in cases of lipidosis, but the atrophy of the olives is unusual. Because of these differences from typical Tay-Sachs disease, the authors regard the condition as an independent form of the disturbance, and although there was no suggestion in the family history of the genetic origin of the disorder, they feel justified in designating it as "congenital amaurotic family idiocy."

N. MALAMUD, Ann Arbor, Mich. [ARCH. NEUROL. & PSYCHIAT.].

Diseases of the Genitourinary Tract

ATTEMPTS TO INDUCE MENSTRUATION BY OPERATIVE ISCHEMIA IN MONKEYS. V. M. EMMEL, R. V. WORTHINGTON and EDGAR ALLEN, Endocrinology **29**:330 (Sept.) 1941.

One of the most striking changes which occurs in the endometrium during the series of events leading to either normal or experimentally induced menstruation is the vasoconstriction and ischemia lasting from four to twenty-four hours just prior to the onset of bleeding. The probability thus exists that during this period of endometrial ischemia changes occur which are responsible for the extravasation of blood following relaxation of the coiled arteries.

In the experiments on monkeys reported here, the circulation to the body of the uterus was completely interrupted for periods varying from one to nineteen hours. This procedure produced no bleeding. The authors point out that this does not invalidate the theory that ischemia limited to the endometrium is an essential antecedent to hemorrhage in normal and experimental menstruation.

JACOBSEN, Buffalo.

UTERINE DISTENTION AND LACTATION. JAMES T. BRADBURY, Endocrinology **29**:393 (Sept.) 1941.

In contradiction to reports by others, Bradbury concludes from experiments on 21 rats that distention of the uterus does not prevent lactation.

JACOBSEN, Buffalo.

PYURIA. J. E. ASHLEY, South. M. J. **34**:742 (July) 1941.

The author reported the following factors to be considered in the treatment of pyuria: (1) elimination of bacteria and their toxins by washing out the urinary tract; (2) increasing the resistance of the patient by proper diet and by specific therapy; (3) medication, acidification and alkalinization of the urine, and (4) elimination of the foci of infection.

In treatment it is of utmost importance to remember that the patient who does not respond to treatment by urinary antisepsis within a reasonable length of time should be suspected of having an anomaly, and further urologic examination should be made.

The author believes sulfonamide compounds have given the greatest aid of any therapeutic measures of this type. While the use of sulfapyridine is limited, sulfathiazole has apparently been of great value against staphylococcic infections as well as infections of other types. A common mistake in the use of these drugs is discontinuance too quickly after the disappearance of pus from the urine.

SCHLUTZ, Chicago.

CHRONIC URINARY INFECTIONS IN CHILDREN. J. M. PACE, South. M. J. **34**:745 (July) 1941.

Pace discusses the importance of a urologic examination in all cases of chronic or recurring infection of the urinary tract.

Obstructive lesions, which are closely associated with chronic or recurring infections, are to be removed with appropriate surgical or urologic methods of treatment.

SCHLUTZ, Chicago.

UROLOGIC ASPECTS OF ENURESIS. H. M. SPENCE, South. M. J. **34**:830 (Aug.) 1941.

Spence believes that a general sizing up of the case by the pediatrician and a brief period of conservative medical treatment will cure the majority of patients with enuresis. If this regimen is unsuccessful, or if at any time pyuria, hematuria, fever or any other symptoms suggesting disease of the genitourinary tract are present, the case should be thoroughly investigated by a urologist.

In the majority of cases of refractory enuresis in girls, a chronic granular urethritis will be found to be the basis. The necessary dilations can be easily carried out by either the urologist or the pediatrician. For refractory enuresis in boys, after major disease and pinpoint meatus are excluded, dilation and instillations are satisfactory.

SCHLUTZ, Chicago.

A CASE OF CONGENITAL BILATERAL RENAL HYPOPLASIA, WITH A SHORT REVIEW OF THE LITERATURE. J. ELLIOT MURRAY and R. A. SANDISON, Brit. M. J. **2**:471 (Oct. 4) 1941.

The authors report a case of bilateral hypoplasia of the kidneys probably of congenital origin. The article begins with a brief review of the literature of congenital renal hypoplasia, hyperplasia and agenesis. It is stated that, while unilateral renal hypoplasia is frequently seen, bilateral congenital renal hypoplasia is rare, as this condition is usually not consistent with life. The case reported is that of a man aged 22 who was in the army and suddenly manifested uremia. An investigation revealed a bilateral renal hypoplasia. Urinary disorders rather suddenly developed, and a steady increase in urea occurred. The diagnosis was made by retrograde pyelography. In this particular case the author states that this man's condition was compatible with life because of the fact that even though the kidneys were severely hypoplastic there was enough kidney tissue to carry on the basic needs of the body. When this article was reported the patient was still alive.

ROYSTER, University, Va.

PYELOGRAPHY AFTER THE SUBCUTANEOUS INJECTION OF DYE. H. MORTENSEN, M. J. Australia **2**:6 (July 5) 1941.

Mortensen reports that excretory urography may be successfully performed after the subcutaneous injection of the usual iodine solutions in diluted form (20 cc. of the solution to be used diluted by the addition of 80 cc. of saline solution). Exposures should be made in ten minutes or twenty minutes, as required subsequently, according to the rapidity of excretion. Slight complaint of pain may be made during the injection, owing probably to the bulk rather than to the irritative nature of the fluid used.

GONCE, Madison, Wis.

REMARKS AND OBSERVATIONS UPON THE ETIOLOGY AND DIAGNOSIS OF RENAL CALCULI. A. C. MCEACHERN, M. J. Australia **2**:55 (July 19) 1941.

In a general discussion on the etiology and diagnosis of renal calculi, the author states that recumbency stones are due to skeletal decalcification (caused by disuse, local hyperemia or toxemia) plus urinary stasis and occur in about 2.1 per cent of patients with poliomyelitis.

GONCE, Madison, Wis.

ENURESIS OF ALLERGIC ORIGIN: A REPORT OF TWO CASES. HOWARD GAUDIN, New Zealand M. J. **40**:242 (Aug.) 1941.

The author reports 2 cases of enuresis clinically suggestive of an allergic origin. The allergen responsible had not been identified, however. Perhaps allergy must be added to the list of factors causative in the development and prolongation of enuresis.

WEIGAND, Indianapolis.

Diseases of the Ductless Glands; Endocrinology

"MAMMOGEN" AND THE TREATMENT OF SPAYED HYPOPHYSECTOMIZED RATS WITH LIPOID EXTRACTS OF CATTLE PITUITARY. ROY O. GREEP and HOMER E. STAVELY, Endocrinology **29**:18 (July) 1941.

The lipid fraction extracted from desiccated cattle pituitaries produced no signs of mammary stimulation in hypophysectomized female rats, while the tissue residue caused definite growth of the lacteal ducts. This material also stimulated body growth.

JACOBSEN, Buffalo.

EFFECT OF INCREASING THE NUMBER OF DAILY INJECTIONS OF GONADOTROPIC PREPARATIONS ON THE OVARIES OF IMMATURE RATS. ROLAND K. MEYER and W. H. MCSHAN, Endocrinology **29**:31 (July) 1941.

A number of different substances which have no gonad-stimulating activity when administered alone have been found to increase the effectiveness of certain pituitary gonadotropic extracts when they are mixed in vitro with the extracts and injected into immature female rats. These augmenters include extracts of urine from normal and from castrate human beings, blood serums from normal and from pregnant women, extracts of milk, beef liver and thyroid, extracts of yeast, casein and egg albumin, leukocytes, zinc and copper salts, formed elements of blood, heme and hemoglobin and chlorophyll.

The effectiveness of pituitary gonadotropic extracts may be increased also by making more frequent injections.

Increasing the number of injections of sheep and beef pituitary gonadotropic extracts from two to twenty-four per day resulted in a large increase in the effect of the extract on the ovaries of immature rats.

The effectiveness of gonadotropic preparations made from pregnant mare's serum, urine of pregnant women and powdered horse pituitaries was not increased by increasing the number of injections from two to twenty-four per day.

JACOBSEN, Buffalo.

ANTIHORMONE PRODUCTION TO CRUDE AND PURIFIED PREGNANT MARE SERUM PREPARATIONS. ALBERT S. GORDON, Endocrinology **29**:35 (July) 1941.

Daily injections into rats of preparations of the serum of pregnant mares for two to five months produced inhibitory antiserums, those formed to the more purified gonadotropic extracts being the most inhibitory. This suggests that the antihormone-evocating factor in pregnant mare's serum is the actual gonadotropin or some chemically related substance.

JACOBSEN, Buffalo.

EFFECTS OF LARGE AMOUNTS OF ANDROGEN ON THE TESTES OF THE PREPUBERAL RAT. R. R. GREENE and M. W. BURRILL, Endocrinology **29**:64 (July) 1941.

As a result of experiments on 15 rats treated with testosterone propionate it was concluded that very large doses of androgens neither stimulate nor depress the testes but maintain them at a normal size.

JACOBSEN, Buffalo.

ABSORPTION OF PELLETS OF CRYSTALLINE TESTOSTERONE, TESTOSTERONE PROPIONATE, METHYL TESTOSTERONE, PROGESTERONE, DESOXYCORTICOSTERONE AND STILBESTROL IMPLANTED IN THE RAT. T. R. FROBES, Endocrinology **29**:70 (July) 1941.

The technic of making and implanting subcutaneously pellets of crystalline preparations of endocrine principles is described. By removing and weighing at intervals pellets implanted in rats it was found that absorption occurred as follows:

Ninety per cent absorption of desoxycorticosterone occurred in twenty-seven days; of testosterone, in thirty-one days; of methyl testosterone, in thirty-six days; of diethylstilbestrol, in fifty-one days; of testosterone monopropionate, in sixty-one days, and of progesterone, in eighty-eight days.

JACOBSEN, Buffalo.

EFFECT OF TESTOSTERONE PROPIONATE UPON REPRODUCTION IN THE FEMALE. JOHN W. HUFFMAN, Endocrinology **29**:77 (July) 1941.

No litters were born to female rats receiving 2 mg. of testosterone daily, but normal pregnancies occurred after cessation of the injections.

JACOBSEN, Buffalo.

EFFECT OF TESTOSTERONE PROPIONATE ON CREATINURIA OF EXPERIMENTAL HYPERTHYROIDISM IN MALE AND FEMALE MONKEYS. JOSEPH W. JAILER, Endocrinology **29**:89 (July) 1941.

The intense creatinuria resulting from administration of thyroxin to monkeys can be suppressed or abolished by administration of testosterone propionate.

JACOBSEN, Buffalo.

EFFECT OF ADMINISTERING THYROTROPIC HORMONE WITH AND WITHOUT IODINE ON THYROID TISSUE METABOLISM. J. E. VANDERLAAN, W. P. VANDERLAAN and M. A. LOGAN, Endocrinology **29**:93 (July) 1941.

The mode of action of iodine in toxic thyroid disease is still a somewhat debatable matter.

Administration of thyrotropic hormone of the pituitary gland to guinea pigs causes hypertrophy of the gland and increased metabolic rate. Administration of iodine with the thyrotropic hormone largely abolishes the increased metabolism of the thyroid gland, although the gland hypertrophies to approximately the same extent as it does in the absence of iodine.

This observation lends strong support to the contention that iodine acts directly to inhibit the metabolic activity of the thyroid gland.

JACOBSEN, Buffalo.

DOES PREGNANCY SUPPRESS THE LACTOGENIC HORMONE OF THE PITUITARY? C. W. TURNER and Joseph MEITES, Endocrinology **29**:165 (Aug.) 1941.

The following theories, based on experimental evidence, have been offered to explain the absence of lactation during pregnancy and its initiation following parturition: (*a*) The placenta produces a suppressing agent during pregnancy which holds lactation in check; (*b*) the mechanical distention of the uterus by the fetus and placenta inhibits lactation; (*c*) the secretion of progesterone by the corpora lutea suppresses lactation during pregnancy; (*d*) during pregnancy the comparatively large amounts of estrogen present in the blood stream inhibit the lactation process (the sudden removal of the inhibition at parturition, due to the diminution of estrogen, is then supposed to provide the stimulus for lactation) and (*e*) the fact that in some animals the amount of lactogenic hormone increases twofold to fourfold following parturition suggests that the primary reason that lactation does not occur during pregnancy is because the level of lactogenic hormone in the pituitary is too low to support lactation.

Experiments on rabbits reported here (assaying lactogen content of pituitaries and placentas) indicate that pregnancy has no inhibitory effect on the lactogenic hormone of the pituitary.

JACOBSEN, Buffalo.

Diseases of the Muscles, Bones, Joints and Lymph Glands

THE EARLIEST ENGLISH EXAMPLE OF BILATERAL CERVICAL RIB. A. J. E. CAVE, Brit. J. Surg. **29**:47 (July) 1941.

Prior to the Anatomy Act of 1832, the only source of legitimate material for dissection was the gallows. The author describes the skeleton of a certain Mary Bateman, who was hanged for murder in 1809, and displays a photograph of the head, neck and shoulders, showing the bilateral cervical ribs. The skeleton now rests in the anatomic museum of Leeds University, where it attracts the anatomist as well as the student of medical history.

KEITH, Toronto, Canada.

DISUSE ATROPHY OF SKELETAL MUSCLES. J. C. ECCLES, M. J. Australia **2**:160 (Aug. 16) 1941.

The muscles of the hindlimbs of 20 cats were rendered completely inactive for several weeks by section of the spinal cord in the upper lumbar region and of all the dorsal roots below this level. The muscles remained flaccid and atrophied because of disuse in 4 animals investigated. Atrophy was prevented in others by tetanizing the motor nerve, this artificial exercise being made as nearly normal as possible. All daily periods of tetanization, from ten seconds to two hours, had a similar effect; in the case of the tibialis anticus and extensor digitorum longus muscles the atrophy was almost prevented; in the case of the gastrocnemius and soleus muscles there was much less effect. The short duration of the stimulation required for prevention of disuse atrophy suggests that the period of stimulation used in electrotherapeutic practice (often one or two hours several times a week) are probably much too long. In patients immobilized in bed a few powerful voluntary contractions per day, allowing lengthening and shortening of the muscles, would probably be sufficient to prevent any extensive atrophy. Similarly in immobilized limbs atrophy might often be preventable.

GONCE, Madison, Wis.

Diseases of the Eye

BAND-SHAPED OPACITY OF THE CORNEA ASSOCIATED WITH JUVENILE ATROPHIC ARTHRITIS. ROBERT T. WONG, Arch. Ophth. **26**:21 (July) 1941.

A case of band-shaped opacity of the cornea in a 13 year old boy suffering from atrophic arthritis is reported. By some this degeneration of the cornea in association with arthritis is considered a definite syndrome. The corneal condition occurs in otherwise healthy eyes.

WESCOTT, Chicago.

EARLY TREATMENT OF SQUINT. O. WILKINSON, South. M. J. **34**:844 (Aug.) 1941.

Wilkinson reports that the first essential in the early treatment of a squint is a proper diagnosis.

After a general observation the degree of squint should be carefully measured, and the presence or absence of refractive defects and visual acuity in each eye should be carefully determined. It is always advisable to measure the squinting child when resting, when tired, when calm and when a bit excited. The near point of convergence should be taken in all cases, as it is of material assistance in detecting an excessive action of an overdeveloped internal rectus muscle.

A proper retinoscopic examination to determine the refractive defect should be done after atropine has been used for about a week.

The author suggests that the degree of squint should be measured while the patient is under the influence of atropine, as an increase in the amount of squint under atropine is an indication for an early operation. The trend in operative correction for squint should be toward strengthening the external rectus muscle by advancement or resection and not toward weakening the internal rectus by too liberal or too numerous recessions.

Since the object of operating early is to restore the child to normalcy, it should be done by a method which will not leave any after-defects which will prevent the normal activity of the eye in after life. SCHLUTZ, Chicago.

Skin Diseases; Allergy

ROENTGEN THERAPY OF HEMANGIOMATA. FRED M. HODGES, L. O. SNEAD and R. A. BERGER, Radiology **36**:700 (June) 1941.

In this article the authors report their results with roentgen therapy and give details of 3 cases, limiting their remarks to the strawberry hemangioma, the cavernous hemangioma and a mixture of these two types.

The first case reported was that of a 6 month old baby girl with a rapidly growing birthmark on the ear and face. It had been previously treated by a dermatologist who had used radium to the point of ulceration, but the lesion was still growing rapidly at the time the authors began to use filtered roentgen rays. With the surrounding normal skin protected with lead, roentgen rays were administered to the region. This treatment was repeated in two weeks, followed by small doses given over a period of thirty months by the method of contact roentgen therapy. By this time the bulkiness of the lesion and most of the discoloration had disappeared.

A second patient, also 6 months of age, had been previously treated by radium for a cavernous hemangioma of the cheek and the upper part of the left arm, in spite of which growth had continued. Treatment as for the former patient was carried out with filtered roentgen rays. A perfect result was obtained on the face, but a flabby fatty mass was subsequently removed surgically from the arm.

In the third case, a child 3 years old had a lesion 3.5 cm. in diameter on the forehead. It had grown slowly from birth. Large doses of roentgen rays were given, as in the 2 preceding cases, and a perfect result was obtained. Although the lesion extended into the eyebrow, the hair was not destroyed.

The authors believe that contact therapy offers radiologists an ideal method for the treatment of certain forms of birthmarks. They believe strongly that in the future this will be the procedure of choice in selected cases of hemangioma and lymphangioma, having observed that it is rapid, safe and efficacious. Contact roentgen therapy is the method of choice for superficial strawberry hemangiomas. Mixed strawberry and cavernous types respond best to a mixture of filtered and unfiltered rays. By using these forms of therapy the authors believe that fewer cases will require supplemental surgery. ANSPACH, Chicago.

Surgery and Orthopedics

SKIN TRANSPLANTATION BY INJECTION. C. GLENN BARBER, Arch. Surg. **43**:21 (July) 1941.

Barber describes a method of transplantation of skin in which minute particles of dermal tissue suspended in saline solution are injected beneath the surface of a granulating wound to stimulate healing of an indolent raw surface. This method has been successfully applied in a number of cases. Its advantages over most of the other methods of free skin transplantation are: that it can be used when mild surface infection is present; that it is applicable to wounds widely variable in size as well as in location, and that it can be used in parts incapable of immobilization.

KAISER, Rochester, N. Y.

FRACTURES OF THE FOREARM AND ELBOW IN CHILDREN. AUGUSTUS THORNDIKE JR. and CHARLES L. DIMMLER JR., New England J. Med. **225**:475 (Sept. 25) 1941.

Beekman and Sullivan report that in a series of over 2,000 fractures in children 75 per cent were in the long bones of the upper extremity, and that the radius was the most frequently fractured long bone in the body. The clavicle has usually been considered to be commonly injured, but it was involved in less than 8 per cent of the fractures in their series.

During the last three and a half years, 364 consecutive fractures of the forearm or elbow have been treated at the Children's Hospital. Of these, 200 involved the distal third of the forearm; 58, the middle and proximal thirds of the forearm, and 106, the elbow, including the head and neck of the radius and olecranon. Dislocations of the distal radial epiphysis are omitted from this series and are more properly included in fractures of the wrist rather than of the forearm.

The methods and position of fixation after reduction and the convalescent care are discussed in detail.

The end results in cases adequately followed up give a very clearcut indication that careful and complete treatment of these fractures, even those involving the elbow, gives good results in more than 94 per cent of the cases.

There was no case of Volkmann's ischemic contracture in this series.

GENGENBACH, Denver.

Miscellaneous

CATHARTICS ARE UNIMPORTANT. HARRY D. GROSSMAN, Arch. Pediat. **58**:509 (Aug.) 1941.

Grossman argues that catharsis produced by drugs, roughage in the diet or enemas is an unnecessary procedure.

ORR, Buffalo.

OAK POISONING: CAUSE REMOVING TREATMENT. EDWIN F. PATTON, California & West. Med. **55**:35 (July) 1941.

The oleoresinous exudate of poison oak which causes the dermatitis acts as an irritant as long as it remains in contact with the skin. It is insoluble in water, hardly soluble at all in alcohol, is partly emulsified by soapsuds but is freely soluble in certain cleaning agents, such as benzine. The use of such a cleansing agent is recommended as a logical and effective treatment. Involved areas are mopped up with cotton pledgets soaked in benzine, which are discarded after use; a certain amount of scrubbing is often advisable. Treatment of fresh lesions is relatively painless; after the skin is broken it becomes increasingly heroic but, according to the author, justifiable because of the results. The treatment may have to be repeated a second or a third time at an interval of a few hours, but regardless of the previous duration of the disease, healing will be well under way in twelve to thirty-six hours. The administration of sedatives is often necessary during the period of treatment.

DAVIS, San Francisco.

STUDIES ON ANAPHYLAXIS IN THE MOUSE. RUSSELL S. WEISER, ORVILLE J. GOLUB and DOROTHY M. HAMRE, J. Infect. Dis. **68**:97 (March-April) 1941.

Experimental evidence is presented which shows that the mouse reacts to active and passive anaphylactic sensitization, desensitization and reversed anaphylaxis. Different strains of mice and individual animals of the same strain were found to vary greatly in their response to active anaphylactic sensitization, a response which exhibited a direct correlation with their precipitin-building capacities but persisted in susceptible mice long after serum precipitins became normal.

Data are presented relative to the influence of size, number, spacing and routes of administration of antigen and immune serums on the rise and duration of active and passive anaphylactic sensitivity in mice. Multiple doses of antigen were found more effective for active sensitization than a single dose. Passive sensitivity following the administration of homologous immune serum persisted longer than when the heterologous immune serum of rabbits was used. Attempts at heterologous passive transfer using immune serum of guinea pigs, rats and chickens failed.

The procedure of greatly increasing the susceptibility of mice to anaphylaxis by adrenalectomy was used in several experiments and proved valuable for detecting low states of sensitivity. It permitted the detection of active sensitivity for at least two hundred and sixty-seven days and passive sensitivity for forty days following sensitization. By this procedure desensitization of the actively sensitized mouse was shown to remain complete for two days, sensitivity returning sharply on the third day.

TOOMEY, Cleveland [AUTHORS' SUMMARY].

A HEMOPHILIA-LIKE DISEASE IN SWINE. A. G. HOGAN, M. E. MUHRER and R. BOGART, Proc. Soc. Exper. Biol. & Med. **48**:217 (Oct.) 1941.

The authors observed a number of swine, closely related, which bled to death either spontaneously or from minor wounds and seemed to have the characteristics of hemophilia of human subjects. The bleeding time from a stab wound was similar for these abnormal animals and for the control swine, but the abnormal animals bled to death when 1 cm. slits were made in the edge of the ear, while in the control swine bleeding stopped in two hundred and fifteen seconds. On the other hand, the coagulation time was prolonged to one hundred and forty-five minutes for the defective animals, as compared with twenty-eight minutes for the normal controls. There was no change in the clot retraction time. The serum calcium and the clotting time were not abnormal. The plasma fibrinogen was slightly less in the defective animals but seemed to be within normal limits. The prothrombin time determined by method of Smith was normal but by the Howell technic was slightly prolonged, which indicated some deficiency in available thromboplastin. The platelet counts were the same in both groups but the platelet volume was greater in the defective animals. Further studies indicated that the platelets were more stable—disintegrated less rapidly. The symptoms resemble hemophilia more closely than any other disease that has come to the attention of these workers.

HANSEN, Minneapolis.

PRODUCTION OF CYTOPLASMIC INCLUSIONS IN LIVER CELLS OF RATS INJECTED WITH CERTAIN PROTEINS. JULIA T. WELD, WILLIAM C. VON GLAHN and LUCY C. MITCHELL, Proc. Soc. Exper. Biol. & Med. **48**:229 (Oct.) 1941.

In a study of 850 rats the authors found cytoplasmic inclusions in the liver cells after injections of hemolytic streptococcus toxin (prepared with either horse or rat serum) as well as of other proteins (sheep serum, sheep serum albumin, sheep serum globulin and horse serum [given to specifically sensitized rats]) but not after injections of normal horse or rat serum, streptococcus toxin (heated to 56 C. for one hour) and horse serum extract of nonhemolytic streptococci.

HANSEN, Minneapolis.

CHORDOMA. W. F. HARVEY and E. K. DAWSON, Edinburgh M. J. **48**:713 (Nov.) 1941.

The writers discuss chordoma and agree that it is probably the only tumor which in its neoplastic proliferation reproduces a purely embryonic tissue. It is now thought to be less rare, possibly owing to a more definite knowledge of its peculiarities and 'ocations. The authors give a table presenting the differential diagnosis of chordoma from chondroma and colloid carcinoma. Chondroma is the commonest of the three in childhood.

NEFF, Kansas City, Mo.

POSOLOGY IN PEDIATRICS. HANS MAUTNER, Ann. pædiat. **157**:65, 1941.

Different physiologic function of the organs of children and of adults may explain the difference in the action of drugs in the two groups.

1. Newborn babies have the ability to live for a short time on a lower oxygen supply than is necessary for adults. This explains the resistance of newborn infants to carbon monoxide intoxication, to strychnine and to other drugs.

2. The different parts of the brain are in a different stage of development. Drugs acting on the underdeveloped cortex, such as caffeine, atropine and pentobarbital, have a mild effect. Drugs acting on subcortical parts, which miss the inhibitory effect of the cortex, show a strong response in young children. An example for those drugs is morphine.

3. In newborn infants the parasympathetic nervous system is in a higher stage of development than the sympathetic nervous system. This explains the resistance of children to epinephrine or atropine and the susceptibility to pilocarpine or to insulin.

4. The different development of the endocrine glands explains the resistance of children to thyroxin and the susceptibility to tuberculosis in time of puberty.

5. The condition of the alimentary canal in young children explains the susceptibility to cathartics. Also the detoxification of the liver of young children is poor.

6. Children are more susceptible to drugs which cause acidosis, like morphine, than to drugs which cause alkalosis, like the stimulant to gastric secretion.

7. Conditions of the development of the musculature may explain the susceptibility of children to ketogenic conditions and also the reaction to digitalis.

AUTHOR'S SUMMARY.

Book Reviews

Hospital Discharge Study: Volume I. Hospitals and Hospital Patients in New York City. By Neva R. Deardorff, Ph.D., and Marta Fraenkel, M.D. Price, $1.00. Pp. 209, with 58 tables. New York: Welfare Council of New York City, 1942.

An analysis of 576,623 patients discharged from hospitals in the city of New York in 1933 brought to light many interesting comparisons. The study was made by the Research Bureau of the Welfare Council of New York City, with the assistance of state and city work relief authorities and the Works Progress Administration.

The three fulfilled objectives were: "(1) To provide a picture of serious sickness conditions in New York City through the analysis of the patients discharged from hospitals in the city during the course of one year; (2) To provide a picture of the demand for hospital care of the various types of service and control from the sick of . . . all age groups, creeds, races, economic and social status; (3) To study the methodological problems attendant upon the various phases of reporting on hospital patients as a routine procedure, particularly to see whether and to what extent hospitals are now able to furnish the necessary data in a complete and uniform way."

Following are some of the most pertinent disclosures of the analysis.

Residence.—In general as well as in special hospitals, the percentage of patients from the "neighborhood" is not large—in general hospitals it varies from 4.1 to 90.4 per cent—propinquity of the hospital apparently exercising little influence. The small proportion of neighborhood patients is true of small as well as of large hospitals. The lowest percentage of patients from nearby is found, naturally, in the special institutions. The lower east side has a consistently high proportion of patients; in the age group of children under 15 years it supplies about three times the rate per thousand as does the borough of Queens. Although generalized statements cannot be made in regard to prevalence of disease of all kinds in the low income districts, findings tend to substantiate the established idea that disease exists with poor living conditions. An exception is the comparatively high rate in Queens Borough of infectional hypertrophy of tonsils and adenoids, but here attention might be brought to the fact that this analysis involves only hospitalized patients.

Diagnostic Data.—Diversity in the practices of recording case histories in various hospitals led to complications in the attempt to get a true picture. However, by counting more than once patients with more than one major diagnosis, the duplicated count revealed the three major disease groups to be: obstetric conditions, conditions of the upper respiratory tract and intestinal conditions. A revealed wide variance in the number of patients treated for given disorders in each of eight hospitals of approximately the same size and census may be due to the degree of eminence of specialists on their staffs.

Demographic Data.—With the exception of the age groups between 15 and 44 years, for whom obstetric care is an important factor, the incidence of hospital service is higher for males. Diagnoses made more frequently for one sex than for the other by at least 20 per cent include: tuberculosis, fractures, stab and gunshot wounds, alcoholism, trauma to brain, deflection of septum, lobar pneumonia, chronic bronchitis, ulcer of stomach, duodental ulcer, hemorrhoids, cirrhosis of the liver, hernia, renal calculus and acute and chronic osteomyelitis, which are more prevalent among males than among females; septicemia, nonmalignant neoplasms, diabetes mellitus, nontoxic goiter, hyperthyroidism, manic-depressive psychoses, psychoneuroses, chronic appendicitis, cholelithiasis, calculus in the common bile duct, acute cholecystitis, chronic cholecystitis, acute peritonitis and acute and chronic cystitis, with which the number of female patients is higher. In

regard to the total patient load, the youngest and oldest groups show the highest figures. Conditions affecting tonsils and adenoids predominate in the group of children under 5 years. The next age group (5 to 14 years) shows a decrease in pneumonia and an increase in fractures and in some of the infectious diseases. From 15 to 34 years there are high figures for obstetric conditions, and for nonmalignant neoplasms; syphilis, gonorrhea and alcoholism gain in importance during this period. In the next ten year period nonmalignant neoplasms and alcoholism reach maximum figures. Patients 45 to 64 years old have more malignant neoplasms, diabetes mellitus, cardiovascular conditions, fractures, benign hypertrophy of the prostate and cataract. Patients over 65 usually seek hospital care for a few major conditions; for more than 24,000 of the 27,507 patients of this group a total of only five ailments were diagnosed—cardiovascular conditions, traumatic conditions and poisonings, cerebral arteriosclerosis and hemorrhage, malignant neoplasms and cataract.

Negro patients constitute 7.5 of the hospital population but only 4.7 of the city's population. While more than three fifths of the white patients discharged were from voluntary hospitals, only one fourth of the Negro patients were cared for in these institutions, and almost all Negroes were treated in wards. Of the total Negro patients in voluntary hospitals, 15.4 per cent paid the full rate charges, 20.2 per cent paid part of the rate, 41 per cent were city charges and 17.7 per cent received free care. Tuberculosis is especially frequent among them. The relatively low proportion of Negroes among patients with scarlet fever, despite sociologic factors, appears as added proof that they are less susceptible to that disease than are white persons.

Analyses by nativity show higher hospital attendance rates for foreign-born than for native-born patients. Among peoples of various national backgrounds, the Czechs have the lowest number of patients and the Irish the highest. Tables show that while the largest religious group among patients is usually that of the hospital's denomination there is a wide interchange. No Protestant hospital has more than 53 per cent of coreligionists. There is a low proportion of Jewish patients in municipal hospitals.

Financial Status of Patients.—Accommodations in private and semiprivate rooms or in wards follow rather closely the apparent economic level of the section of the city from which the patient comes. Approximately 80 per cent of the total discharged patients and 73 per cent of the patients discharged from voluntary hospitals were cared for in wards, the remainder being nearly equally divided between private and semiprivate accommodations. Data for Jewish hospitals show a high proportion of private and semiprivate rooms, with an avoidance of admission to wards among that nationality. Even in times of economic hardship, more than one third of the ward patients are shown to have paid in full for their care and another 12.9 per cent paid in part. Endowments and charitable procedures make possible free care for 8.2 per cent of the private and semiprivate patients. Nearly 60 per cent of the patients discharged whose pay status was known received their care at the expense of the community.

Length of Stay in the Hospital.—The total number of patient-days recorded in the study show an average length of stay of seventeen and five-tenths days; if the chronically ill are omitted, the length of stay is sixteen and nine-tenths days. Seventy-two and seven-tenths per cent of all patients are discharged after a stay of less than two weeks. Ninety-four and four-tenths per cent of patients are discharged alive. Deaths occur in the largest proportions in the short stays and in the long stays in the hospital. Full pay and part pay patients tend to make shorter stays than nonpaying patients. The proportion of patients readmitted to the same hospital does not exceed 4.5 per cent of the total number admitted to all hospitals during the year. Of the total number of discharged patients, at least 2.9 per cent were transferred to other hospitals.

Mortality Among Hospital Patients.—Under a four point classification, the status at discharge was as follows: 36.2 per cent cured, 46.8 per cent improved, 7.6 per cent unimproved and 5.6 per cent dead. The male death rate is higher than the female for the age groups not affected by obstetric conditions as well as

for those age periods. Death in the hospital occurred in nearly 20 per cent of the cases of tuberculosis, in 25 per cent of the cases of malignant neoplasms, in 34 per cent of the cases of cirrhosis of the liver and in 38 per cent of the cases of cerebral arteriosclerosis and hemorrhage; chances for survival of patients with bronchopneumonia are 58 per cent and for patients with septicemia 39 per cent. More than 50 per cent of the total deaths in hospitals occur within the first week after admission, and it may be assumed that a considerable proportion occur on the first day.

Keep Them Human. By C. Madeliene Dixon. Price, $1.50. Pp. 156, with no illustrations. New York: John Day Co., Inc., 1942.

Play has long been recognized as an important factor in the growth and development of children. Until the last few years there have been few good practical books which parents and teachers could use in this work. "Keep Them Human" is the fourth valuable book written on play for children from 4 to 8 years of age by C. Madeleine Dixon; it was written after many years of observation and study by the author in nursery schools.

The first part of the book deals with play in wartime. It describes in detail the methods by which the normal "war play" of children can be utilized to develop constructive, useful activities in children and at the same time give them an opportunity to express themselves freely. The remainder of the book discusses play in general.

The book is well written; it is clear, concise, interesting and helpful to the pediatrician and the teacher. It is the kind of book that should be recommended to all parents of young children.

Epidemiologia del kala-azar infantil. By José Boix Barrios. Price, not given. Pp. 30, with 2 illustrations. Valencia, Spain: Tipografía Pascual Quiles, 1942.

This monograph is an interesting study by the chief of the hygiene service of the province of Castellón de la Plana. Kala-azar is frequent in Mediterranean countries and especially in the provinces of Spain bordering the Mediterranean. It is essentially a rural infection, and in the majority of instances the presence of infected animals about the patient can be demonstrated. It cannot be entirely established that transmission is by members of the genus Phlebotomus. An excellent bibliography is given.

La vacunacion antituberculosa con el B. C. G. By Alberto Chattas. Price, not given. Corodoba: Imprenta de la Universidad, 1942.

This is a well written and well organized book in Spanish on BCG vaccination. The author discusses the frequency of tuberculosis in Argentina and its method of control by BCG vaccination. The exact technic is given in great detail, with photographs of the various types of reactions and complications. The results are clearly tabulated, and there is an excellent résumé of various studies throughout the world on BCG vaccination.

News and Comment

NOTICE

American Board of Pediatrics.—The American Board of Pediatrics announces that on July 1, 1943, group I (physicians who have specialized in pediatrics for ten years or more) will be abolished.